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Ethics Advisory Board

Department of Health,
Education, and Welfare

Report and Conclusions:

HEW Support of Research Involving Human *In Vitro* Fertilization and Embryo Transfer

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PREFACE

Current regulations of the Department of Health, Education, and Welfare (HEW) prohibit the support of research involving the fertilization of a woman's egg (ovum) outside her body (in vitro fertilization) until the Ethics Advisory Board has advised the Secretary as to its ethical acceptability. In 1977, the Department received an application for support of such research and, after it had been approved from a scientific point of view, forwarded it to the Board. At its meeting in May 1978, the Board agreed to review the research proposal.

Over the summer, the announcement of the birth of a baby following in vitro fertilization in England aroused great public interest; it appears that a number of couples are ready and eager to avail themselves of such procedures in order to overcome infertility. Therefore, in September, Secretary Califano asked the Board to broaden its consideration of the pending application to include the scientific, ethical, legal and social issues surrounding human in vitro fertilization and embryo transfer in general.

This report is the result of over a half a year of study during which the Board asked scholars and experts in the fields of reproductive science, ethics, theology, law and the social sciences, to prepare reports and discuss the issues with Board members in public meetings. In addition, the Board held a series of eleven public hearings throughout the country in which private individuals, professional societies and public interest groups had an opportunity to present their views. The Board also received over 2,000 pieces of correspondence including letters, postcards and formal testimony, all of which were copied and distributed to each of the members.

Chapter I of the Report provides background information about the human reproductive process and research involving *in vitro* fertilization and embryo transfer. Chapter II explores the technical and ethical issues surrounding such research in humans and Chapter III addresses the technical and ethical issues surrounding the use of the procedures in clinical practice. Chapter IV presents a review of the legal issues, and Chapter V summarizes public attitudes as presented to the board and as determined by recent public opinion polls. The Board's conclusions are set forth in Chapter VI.

The Board hopes that its deliberations and conclusions will be useful to the Secretary and staff of the Department in making decisions regarding the support and conduct of research involving human *in vitro* fertilization and embryo transfer.

* * * * *

An appendix containing papers prepared for the Board by scholars in the fields of reproductive science, ethics, theology, law, statistics, and social policy will be available through the U.S. Government Printing Office. Ordering information may be obtained from the Ethics Advisory Board, Westwood Building, Room 125, 5333 Westbard Avenue, Bethesda, Maryland 20016, telephone: (301) 496-7776.

CHAPTER I: BACKGROUND

A. The Normal Human Reproductive Process

Through long years of painstaking study reproductive biologists have been able to acquire significant information concerning the human reproductive process. The gathering of data on this process has presented formidable obstacles, since fertilization and the earliest days of embryonic development occur within the woman's body where, for both technical and ethical reasons, they are not readily accessible for scientific study.

According to the best available evidence, for the average couple the performance of the human reproductive system is only partially "efficient." That is, not every meeting of sperm and ovum results in the production of a viable embryo. One study estimates that in 16% of the cases where human ova are exposed to sperm, fertilization fails to occur. When fertilization does occur, the rate of embryonic loss during the first week is estimated to be 18% and in the second week an additional 32%. According to this study, only 37% of human zygotes survive to be delivered subsequently as live infants.[1] Statistical surveys of the length of time generally required to establish a pregnancy seem to lend support to these estimates.[2]

These relatively high rates of embryonic loss are due in part to external environmental factors which impede continued embryonic development and in part to chromosomal or genetic abnormalities in the embryo

itself. The exact proportion of embryonic loss due to each of these factors is unknown. However, one study estimates that perhaps 50% of the embryonic loss subsequent to successful fertilization is due to chromosomal aberrations.[3] Thus, natural selection against most embryos with serious chromosomal abnormalities seems to occur during pregnancy, particularly during the first eight weeks following fertilization.

B. Previous Research with and Application of In Vitro Fertilization and/or Embryo Transfer

1. General

In previous research with humans and other species three major techniques have been employed: (a) in vitro fertilization without subsequent transfer of the embryo to the uterus of a female; (b) in vitro fertilization followed by embryo transfer; and (c) embryo transfer following fertilization by mating or artificial insemination. Only the first and second techniques have been employed with human beings.

For in vitro fertilization (in either the first or second cases listed above) a method must be found for harvesting ova from the female and for bringing the ova into contact with sperm from the male in the laboratory setting. In human beings ova are usually secured from the female by means of a surgical procedure called laparoscopy. A needle is passed through the woman's navel and brought into proximity to one or both of her ovaries. Through visual sighting follicles containing mature ova are located, and the ova are removed from the follicles by means of the needle. Human females normally produce only one mature ovum per menstrual cycle; however, if certain hormones are administered early in a given menstrual cycle, multiple ova are produced which can then be harvested during a single laparoscopic procedure.

Following the successful harvesting of ova, the ova and sperm from a male are placed in a laboratory medium where ova and sperm complete maturation and fertilization occurs. The early embryo is then transferred to a different laboratory medium for subsequent growth. In the first case noted above the embryo is retained in culture in the laboratory setting. In the second case the embryo is transferred to the uterus of a female -- either the female donor of the ova or another female whose hormonal cycle is at approximately the same stage as the cycle of the donor female. If the transfer is successful, implantation and subsequent development of the embryo occur in the uterus of the recipient female.

In the third case fertilization occurs in vivo in the animal, either through mating or through artificial insemination. The ova may be either those of the inseminated female or those of a donor. Following fertilization but prior to implantation, the resulting embryo or embryos are removed from the reproductive tract of the female and are transferred to the reproductive tract(s) of one or more recipient females. If the transfer is successful, implantation and subsequent embryonic development occur in the recipient female(s).

In summary, the following combinations of in vitro fertilization and/or embryo transfer are possible:

i. In vitro fertilization without embryo transfer

ii. In vitro fertilization and subsequent embryo transfer

   a. Transfer to the uterus of the donor
   b. Transfer to the uterus of one or more other females

iii. *In vivo* fertilization and subsequent embryo transfer

a. Fertilization by means of mating
b. Fertilization by means of artificial insemination
c. Ova of the mated or inseminated female
d. Donor ova introduced into the female prior to fertlization

2. Research and Applications with Animal Species

a. Nonprimate Laboratory Animals. Successful laboratory experiments with embryo transfer of early rabbit embryos predated by almost 70 years the first successful experiment with *in vitro* fertilization. In 1890 Walter Heape -- working in Cambridge, England -- succeeded in transferring two embryos from an Angora doe rabbit which had been mated with an Angora buck into the oviduct of a Belgian hare doe which had itself mated several hours before. Six offspring were born to the Belgian hare doe, of which two were clearly Angoras.[4] A similar technique was applied to cultured mouse blastocysts in 1958 by Anne McClaren and John D. Biggers. Some of the offspring grew to adulthood and reproduced naturally to yield a second generation.[5]

Between 1930 and 1959 many investigators sought to imitate the process of embryonic development in the laboratory setting by means of *in vitro* fertilization. However, the researchers failed to devise sufficiently stringent criteria to demonstrate that early embryonic development was indeed the result of fertilization of ova by sperm rather than the effect of laboratory manipulation of the unfertilized ovum. (Severe trauma to the ovum, *e.g.*, puncture or electric shock, can in some cases induce cell division without fertilization). In 1959, however, M.C. Chang of the Worcester Foundation in Massachusetts succeeded in documenting *in vitro* fertilization in the rabbit by taking sperm from

male rabbits with specific traits not present in the female ovum donor. The presence of the male traits in the offspring (following embryo transfer and subsequent development) provided unequivocal proof that the sperm had indeed transmitted genetic information to the offspring.[6]

Since 1933 there have been 5 published studies of embryo transfer following *in vivo* fertilization in rabbits, 3 in rats, and 1 in mice.[7] From 1959 to the present, 13 papers (including Chang's initial paper) on *in vitro* fertilization followed by embryo transfer in rabbits have been published, 8 papers on the same procedure in mice, and 1 in rats. In 3 of those studies, 1 on rats and 2 on rabbits, abnormal offspring were reported; however, the causes of the abnormalities are unknown.[8]

Many studies in experimental embryology do not include embryo transfer as a component; rather, they involve various types of laboratory investigation of the early embryo -- whether produced by *in vivo* or *in vitro* fertilization. These non-transfer studies examine such topics as mechanisms of normal and abnormal fertilization; the earliest stages of embryonic development; causes of abnormality in early embryos; and the effect of various environmental factors, *e.g.*, radiation, freezing, and various chemicals, on fertilization and early development.[9] Research techniques employed in the study of these topics include fertilization *in vitro*; *in vitro* culture of early embryos to and beyond the blastocyst stage; the fusion of embryonic cells with other cells; the infection of embryonic cells with viruses; the introduction of various changes (chemical or temperature changes, for example) into the embryonic environment; biochemical studies of embryonic cells; and microscopic analysis of embryonic cells.[10]

The technique of superovulation -- that is, the administration of a hormone which induces the female to produce a larger than usual number of ova -- has sometimes been employed in conjunction with in vitro fertilization. Superovulation has been studied rather extensively in rabbits. In one controlled comparison of normally ovulated and superovulated oocytes (total number = 538) 60.1% of embryos obtained following superovulation and 54.6% of those obtained following normal ovulation developed into normal young.[11] In contrast, several other studies in rabbits, as well as in mice, have concluded that an increase in the incidence of chromosomal aberrations occurs following superovulation.[12]

The effects of freezing mammalian embryos have also been studied in considerable detail. The most studied species is the mouse. In one study mouse embryos stored at -195° C for 369 days were cultured and transferred after having been frozen and thawed. The freezing process caused some cellular damage, as evidenced by the fact that a smaller percentage of frozen embryos survived than did unfrozen controls. However, previously frozen offspring were normal and grew and reproduced at the same rate as control animals. The second-generation progeny of the frozen embryos were also normal.[13]

b. Farm Animals. In research with farm animals -- particularly, cows, horses, sheep, goats, and pigs -- the primary emphasis has been on application rather than on the development of basic knowledge. For this reason, more work has been done on embryo transfer following in vivo fertilization than on in vitro fertilization itself. Research both with in vitro fertlization and with embryo transfer is dwarfed by the use of artificial insemination for commercial breeding purposes: with the aid of

artificial insemination no fewer than 100,000,000 cattle have been produced in the United States alone.[14]

Relatively little laboratory research with in vitro fertilization or with in vivo fertilization using donated ova has been performed in farm animals. Five successful studies in cattle, three in sheep, and one in pigs have been reported.[15]

In contrast, embryo transfer following in vivo fertilization of the female's own ova has been widely employed, primarily in cattle, during the past five years. Indeed, thousands of progeny have been produced by this method. Techniques for recovering early embryos from the female following fertilization include both surgical and nonsurgical means. Offspring from embryo transfer appear to be normal, although no carefully controlled study of the outcome of pregnancy has been undertaken.[16]

Two additional techniques which can be employed in conjunction with in vitro fertilization and/or embryo transfer have been studied in farm animals. In two studies efforts were made to evaluate the overall quality of early cattle embryos by examining them for compactness, symmetry, and density. These subjective qualitative assessments were successful in predicting differential rates of subsequent pregnancy.[17] A second technique which has been employed experimentally with cattle embryos is the determination of sex through removing cells from the trophoblastic layer of the early embryo. However, many embryos are damaged in the process of sex determination.[18]

c. Non-Human Primates. Relatively little research on in vitro fertilization and/or embryo transfer has been performed with non-human primates. Three studies beginning with that of Gould and associates

in 1973[19] and continuing with the work of Dukelow and Kuehl[20] have demonstrated fertilization in vitro with the squirrel monkey. In vitro fertilization studies with the Olive baboon and the rhesus monkey have not yet provided definitive proof that fertilization has in fact occurred. However, in 1976 D.C. Kraemer and associates reported the successful transfer of an embryo from an Olive babboon to a synchronized female following in vivo fertilization.[21] Similarly, in 1977 J.H. Marston and associates reported a successful embryo transfer from one oviduct to the other in a female rhesus monkey after in vivo fertilization.[22]

The meager data from primate research may reflect technical and funding limitatons on the one hand, or a lack of interest or incentive on the other. Gould has noted that primate research is expensive and that the competition for research funds is a limiting factor. He further observes that investigators may be confronting "as yet unidentified problems regarding the culture requirements for successful maintenance on nonhuman primate gametes in vitro."[23] By contrast, Sackett and Smith have expressed confidence that there would be no problem in obtaining a sufficient number of primates to undertake research in this area; further, they report that reliable normative data regarding fertilization, pregnancy, and early development exist against which to measure deviations from the norm resulting from in vitro fertilization and embryo transfer.[24]

3. Research and Applications in Humans

Most successful human research has been concentrated on achieving in vitro fertilization and on culturing early human embryos in the laboratory. Efforts at clinical application of in vitro fertilization and embryo transfer to overcome infertility were notably unsuccessful

until the latter half of 1978 and early 1979 when the delivery of three apparently healthy infants following these procedures was announced.

The first well documented achievement of in vitro fertilization with human gametes was reported in 1970 by R.G. Edwards, P.C. Steptoe, and J.M. Purdy.[25] Since 1970 there have been seven additional scientific reports of successful in vitro fertilization -- four by R.G. Edwards and his colleagues,[26] two by A. Lopata and associates in Australia,[27] and one by Soupart and Strong in the United States.[28] No details concerning the apparently successful in vitro fertilization in Calcutta, India, have been published.

Embryo transfer in humans has been attempted only following in vitro fertilization. A total of three reports of such efforts have appeared in the scientific literature, one by the Australian group (in 1973),[29] and two by Edwards and Steptoe (in 1976 and 1978).[30] The first attempt led to raised levels of human chorionic gonadotropin in the maternal blood, but implantation was not documented. The second resulted in an ectopic pregnancy in one of the woman's Fallopian tubes. As is well known, the third reported attempt culminated in the birth of a female infant. In oral presentations to scientific meetings, Edwards and Steptoe have reported the birth of a second healthy child, a male, as well as the occurrence of spontaneous abortions in two additional pregnancies initiated by means of in vitro fertilization and embryo transfer. The four pregnancies reported by Edwards and Steptoe followed 32 attempts at embryo transfer.[31] In addition, the birth of a female child in India following in vitro fertilization and embryo tranfer has been reported in the press.[32]

The potential risks of several aspects of human *in vitro* fertilization and embryo transfer have received some discussion in the scientific literature. The technique of superovulation is frequently (though not necessarily) employed in efforts to recover multiple oocytes for *in vitro* fertilization. One report indicates that the technique of superovulation may be associated with higher rates of a chromosomal abnormality (trisomy) in humans.[33] Similarly, evidence from research with mice suggests that too-high a concentration of sperm around the ovum *in vitro* may result in its fertilization by multiple sperm and thus lead to another type of abnormality (triploidy) in the embryo.[34]

In vitro fertilization techniques may also bypass a natural screening process to which sperm are subjected in human reproduction *in vivo*. There is some evidence to indicate that the female reproductive tract selectively eliminates many abnormal sperm. In one study of the human Fallopian tube, for example, it was demonstrated that few morphologically abnormal sperm reach the site of fertilization.[35] Similar observations have been made in studies of mice.[36] The extent of this risk, as well as the two types of risks noted in the preceding paragraph, is unknown.

Two other theoretical sources of risk to human embryos have not been documented in research performed to date: the risk of inducing point mutation or teratogenic effects in the early embryo.[37] The mammalian embryo is highly resistant to environmental insults. Massive insults generally kill rather than merely damage the preimplantation embryo.

These five types of potential risks in humans are, at present, either theoretical or hypothesized on the basis of rather limited data. In addition, even if superovulation or *in vitro* fertilization were to

produce a chromosomally or genetically abnormal embryo, there is only a low probability that such an embryo would develop to term. The natural process by which most abnormal early embryos are lost during the early weeks of pregnancy would presumably be operative following in vitro fertilization, as well.

C. The First Phase of the Ethical Debate

Within the American context, the public debate concerning ethical aspects of in vitro fertilization was initiated by biologist James Watson. In an extended statement presented in January 1971 to the Panel on Science and Technology of the House Committee on Science and Astronautics, Watson expressed concern that research advances in human in vitro fertilization and the cloning of frogs could in the future lead to attempts to clone human beings.[38] Watson's views were given wide circulation through being excerpted in the May 1971 issue of Atlantic magazine.[39]

An essay defending in vitro fertilization appeared in Nature in May 1971 -- the same month that Watson's comments were published in the Atlantic. The Nature essay, written by British biologist R.G. Edwards and American lawyer David Sharpe, indicated potential benefits of in vitro fertilization research and advocated interdisciplinary consultation as the best method for social monitoring of the research.[40]

In late 1971 and the first half of 1972, ethical critiques of in vitro fertilization were eloquently presented by biologist-philosopher Leon Kass and theologian Paul Ramsey. The essays of Ramsey and Kass, published in leading medical and public-policy journals, questioned the means being employed in in vitro fertilization research and voiced

concern about the potential future applications of the research.[41,42] In announcing that it would publish the Ramsey essay, the Journal of the American Medical Association editorially called for a moratorium on human in vitro fertilization research.[43]

From mid-1972 to early 1974 relatively little ethical analysis of in vitro fertilization was published. A Ciba Foundation symposium on "The Law and Ethics of AID and Embryo Transfer" was held in 1972.[44] In an invitational symposium published in the November 1973 issue of the Journal of Reproductive Medicine, several authors -- including veterinarian Benjamin Brackett, ethicist Joseph Fletcher, and physicians Luigi Mastroianni and Landrum Shettles -- presented sharply divergent viewpoints.[45] In addition, the Committee on the Life Sciences and Social Policy of the National Research Council, whose executive secretary was Leon Kass, completed a detailed technology assessment of in vitro fertilization in 1973. Publication of the report was delayed until 1975.[46]

In 1974 the ethical discussion of in vitro fertilization seemed to revive. Biologist R.G. Edwards published an extensive survey of medical, ethical, and legal questions surrounding the technique. Edwards devoted particular attention to answering the ethical objections which had previously been raised by Kass and Ramsey.[47] During the same year Joseph Fletcher published The Ethics of Genetic Control. In this work Fletcher affirmed the value, indeed the superiority, of numerous genetic and reproductive technologies, including in vitro fertilization, as compared with the conventional method of human reproduction.[48]

Between the publication of the National Research Council's technology assessment in 1975 and the middle of 1978 little new ethical literature on in vitro fertilization appeared. The first phase in the ethical debate on in vitro fertilization thus concluded with a pause. Not until the birth of a child conceived with the aid of the technique did the pause end and the second phase of the ethical debate begin.

D. The Evolution of HEW Involvement

HEW involvement in setting guidelines for research involving in vitro fertilization and/or embryo transfer has resulted in the publication of three documents: a "draft working document of proposed policy" (November 16, 1973);[49] a set of proposed regulations (August 23, 1974);[50] and final regulations (August 8, 1975).[51] It is perhaps worthy of note that the questions of fetal research, research with pregnant women, and research involving children received substantially greater attention in the three HEW documents than did the issue of in vitro fertilization. This differential allocation of attention accurately reflected the public-policy setting of 1973, when fetal research, in particular, was a matter of significant public controversy. The relative de-emphasis of in vitro fertilization in the HEW guidelines also reflected the view that successful embryo transfer in humans was not likely to be technically feasible in the near future.

The successive versions of HEW guidelines and rules published between 1973 and 1975 tended toward less detail in their stipulations and toward a greater emphasis on a review procedure for proposed research with human in vitro fertilization and/or embryo transfer. The 1973 draft policy stipulated that:

1. "Care must be taken not to bring human ova fertilized *in vitro* to viability.... "

2. "All proposals for research involving human *in vitro* fertilization must be reviewed by the Ethical Review Board."

3. "No research involving the implantation of human ova fertilized in the laboratory into recipient women should be supported until the appropriate scientific review boards are satisfied that there has been sufficient work in animals (including sub-human primates) to demonstrate the safety of the technique. It is recommended that this determination of safety include studies of natural born offspring of the products of *in vitro* fertilization."

4. "No implantation of human ova fertilized in the laboratory should be attempted until guidelines are developed governing the responsibilities of the donor and recipient 'parents' and of research institutions and personnel."[52]

In August 1974, subsequent to the passage of legislation establishing the National Commission for the Protection of Human Subjects but prior to the Commission's first meeting, HEW published proposed rule-making on research with several specific groups of human subjects. This document responded to comments on the November 16, 1973 preliminary draft regarding *in vitro* fertilization research, clarified the definition of a fetus, and suggested issues to be considered by the Ethical Advisory Board in its review of any proposed HEW supported research involving human *in vitro* fertilization or embryo transfer. In this 1974 document "fetus" was defined to include "both the product of *in vivo* conception and the product of *in vitro* fertilization which is subsequently implanted in the donor of the ovum."[53] With respect to unimplanted human embryos, the 1974 rules proposed no specific guidelines.

However, the 1974 HEW document recommended that the Ethical Advisory Board take into account certain issues in reviewing research proposals involving *in vitro* fertilization and/or embryo transfer:

> With respect to the fertilization of human ova *in vitro*, it is expected that the Board will consider the extent to which current technology permits the continued development of such ova, as well as the legal and ethical issues surrounding the initiation and disposition of the products of such research.
>
> With respect to implantation of fertilized human ova, it is expected that the Board will consider such factors as the safety of the technique (with respect to offspring) as demonstrated in animal studies, and clarification of the legal responsibilities of the donor and recipient parent(s) as well as the research personnel.[54]

In August 1975, HEW responded to the National Commission's report and recommendations concerning fetal research. Since the Commission had not specifically addressed the issue of research involving *in vitro* fertilization and/or embryo transfer, HEW chose not to promulgate substantive regulations governing such research. It did, however, clearly reiterate a procedural requirement:

> (e) No application or proposal involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.[55]

The effect of this review requirement between August 1975 and September 1977, when the Ethics Advisory Board was appointed by HEW Secretary Califano, was to place a *de facto* moratorium on all HEW supported human research involving *in vitro* fertilization and/or embryo transfer.

FOOTNOTES

1. Biggers, John D., In Vitro Fertilization, Embryo Culture and Embryo Transfer in the Human, a paper prepared for the Ethics Advisory Board, 1978, Table 2, p. 10, citing Leridon, H., Demographie des Echers de la Reproduction, in: Boue, A. and Thibault, C., eds., Les Accidents Chromosomiques de la Reproduction, Paris, Centre International de l'Enfance, 1973, pp. 13-27.

2. Biggers, op. cit., p. 11, citing Roberts, C.J. and Lowe, C.R., Where Have all the Conceptions Gone?, Lancet, vol. i, pp. 498-499, 1975.

3. Biggers, op. cit., p. 13, citing Boue, J.G. and Boue, A., Chromosomal Anomalies in Early Spontaneous Abortion, Current Topics in Pathology, vol. 62, 1976, pp. 193-208.

4. Biggers, op. cit., p. 19, citing Heape, W., Preliminary Note on the Transplantation and Growth of Mammalian Ova with a Uterine Foster-mother, Proceedings of the Royal Society, vol. 48, 1890, pp. 457-458.

5. Biggers, op. cit., p. 19, citing McLaren, A. and Biggers, J.D., Successful Development and Birth of Mice Cultivated In Vitro as Early Embryos, Nature, vol. 182, 1959, pp. 877-878.

6. Biggers, op. cit., p. 20, citing Chang, M.C., Fertilization of Rabbit Ova In Vitro, Nature, vol. 184, 1959, pp. 466-467.

7. Rice, Catherine, Supplement to: In Vitro Fertilization, Embryo Culture and Embryo Transfer in the Human by John D. Biggers, 1978, Table 1, pp 1-6.

8. Biggers, op. cit., Table 7, p. 40.

9. Ibid., Table 3, p. 22; see also Walters, LeRoy, Ethical Issues in Human In Vitro Fertilization and Research Involving Early Human Embryos, a paper prepared for the Ethics Advisory Board, 1978, p. 32, citing Fowler, Ruth E. and Edwards R.G., The Genetics of Early Human Development, in: Steinberg, Arthur G. and Bearn, Alexander G., eds., Progress in Medical Genetics, Vol. IX, New York, Grune and Stratton, 1973, pp. 92-95; Karp, L.E. and Donahue, R.P., Preimplantational Ectogenesis -- Science and Speculation Concerning In Vitro Fertilization and Related Procedures (Medical Progress), Western Journal of Medicine, vol. 124, p. 296, April 1976; National Research Council, Assembly of Behavioral and Social Sciences, Committee on the Life Sciences and Social Policy, Assessing Biomedical Technologies: An Inquiry Into the Nature of the Process, Washington, D.C., National Academy of Sciences, 1975, p. 27.

10. Culture of human embryos beyond the blastocyst stage has not yet been reported in the scientific literature. Walters, op. cit., p. 32. The use of several of these techniques in research with non-human embryos is described by Edwards, R.G., Fertilization of Human Eggs In Vitro: Morals, Ethics, and the Law, Quarterly Review of Biology, vol. 49, March, 1974, pp. 3-6.

11. Foote, Robert H., In Vitro Fertilization in Perspective, Relative to the Science and Art of Domestic Animal Reproduction, a paper prepared for the Ethics Advisory Board, 1978, p. 6, citing Maurer, R.R., Hunt, W.L., Van Vleck, L.D., and Foote, R.H., Developmental Potential of Superovulated Rabbit Ova, Journal of Reproduction and Fertility, vol. 15, 1968, pp. 171-175.

12. Biggers, op. cit., p. 33, citing Fujimoto, S., Pahlaven, N. and Dukelow, W.R., Chromosome Abnormalities in Rabbit Preimplantation Blastocysts Induced by Superovulation, Journal of Reproduction and Fertility, vol. 40, 1974, pp. 177-181; Fujimoto, S., Passantino, T.J., and Koenczoel, I., A Preliminary Note on Chromosome Abnormalities in Intratubal Rabbit Embryos, Proceedings of the Japanese Academy, vol. 51, 1975, pp. 51-55; Takagi, N., and Sasaki, M., Digynic Triploidy After Superovulation in Mice, Nature, vol. 264, 1976, pp. 278-281; Maudlin, I., and Fraser, L.R., The Effect of PMSG Dose on the Incidence of Chromosomal Anomalies in Mouse Embryos Fertlized In Vitro, Journal of Reproduction and Fertility, vol. 50, 1977, pp. 275-280.

13. Foote, op. cit. p. 16, citing Maurer, R.R., Bank, H., and Staples R.E., Pre- and Postnatal Development of Mouse Embryos After Storage for Different Periods at Cryogenic Temperatures, Biology of Reproduction, vol. 16, 1977, pp. 139-146.

14. Foote, op. cit., p. 5.

15. Ibid., pp. 10-14.

16. Ibid., p. 17, citing Betteridge, K.J., ed., Embryo Transfer in Farm Animals, Ottawa, Ontario, Canada Department of Agriculture, Monograph, vol. 16, 1977.

17. Foote, op. cit., p. 18, citing Shea, B.F., Hines, D.J., Lightfoot, D.E., Ollis, G.W., and Olson, S.M., The Transfer of Bovine Embryos, in: Rowson, L.E.A., ed., Egg Transfer in Cattle, Luxembourg, Commission of European Communities, EUR 5491, 1976, pp. 145-152; Elsden, R.P., Nelson, L.D., and Seidel, G.E., Jr., Superovulation of Cows with Follicle Stimulating Hormone and Pregnant Mare's Serum Gonadotropin, Theriogenology, vol. 9, 1978, pp. 17-26.

18. Foote, op. cit., p. 19, citing Hare, W.C.D. and Betteridge, K.H., Relationship of Embryo Sexing to Other Methods of Prenatal Sex Determination in Farm Animals: A Review, Theriogenology, vol. 9, 1978, pp. 27-43.

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CHAPTER II: LABORATORY RESEARCH INVOLVING HUMAN IN VITRO FERTILIZATION AND/OR THE CULTURE OF EARLY HUMAN EMBRYOS: TECHNICAL AND ETHICAL ISSUES

The technical and ethical issues surrounding in vitro fertilization using human gametes depend, to some extent, on whether or not the procedure is performed with the intent of transferring the resulting embryos to women for further development. The discussion in this chapter relates to in vitro fertilization of human ova when there is no intention of transferring the product to establish a pregnancy. Chapter III deals with human in vitro fertilization performed with the specific intent of initiating a pregnancy.

These two chapters focus primary attention on technical and ethical issues as presented to the Ethics Advisory Board in papers prepared by its consultants. Thus, they do not summarize the primary scientific and ethical publications concerning in vitro fertilization and/or embryo transfer.

In one of the papers prepared at the request of the Board, LeRoy Walters surveyed the ethical literature on in vitro fertilization published through August 1978.[1] This survey noted that most of the ethical discussion on in vitro fertilization has concentrated on clinical applications of the technique (the topic of Chapter III) rather than on laboratory research with early human embryos (the topic of the present chapter). Central issues in the ethical literature on basic research with human embryos included the moral status of the early embryo, the need for such research, and the potential long-term consequences of the research. According to the same survey, commentators on ethical issues in the

application of in vitro fertilization and/or embryo transfer discussed, among other topics, the need for in vitro fertilization as a method for overcoming infertility, the adequacy of prior laboratory and animal research, the risks of in vitro fertilization and embryo transfer to the ovum donor as well as to potential offspring, and the appropriateness of allocating scarce health care resources to the clinical application of such techniques. Many of these issues recurred in the papers presented to the Board, which are systematically reviewed in this and the following chapter.

A. The Goals and Potential Benefits of the Research

As noted in the preceding chapter many studies in experimental embryology do not include embryo transfer as a component. Several possible goals of laboratory research with human embryos have been identified:

1. Developing or testing more adequate contraceptives;[2]
2. Determining causes of infertility;[3]
3. Investigating the circumstances leading to the development of hyatidiform moles and their potential transformation into malignant tumors;[4]
4. Evaluating the effect of noxious agents or teratogens on the early embryo by means of an in vitro screening system;[5]
5. Studying the mechanisms by which chromosomal abnormalities are produced;[6] and
6. Investigating the totipotential cells of very early embryos to increase understanding of normal and abnormal cell growth and differentiation.[7]

One additional potential goal of human *in vitro* fertilization and embryo culture is more controversial and therefore merits more detailed comment. R.V. Short suggests that a kind of *in vitro* assessment (or "toxicology testing") study might be performed to determine whether *in vitro* fertilization produces a higher incidence of embryonic abnormalities than the conventional *in vivo* method of human reproduction. In Short's view, if *in vitro* fertilization techniques do in fact lead to an excess of embryonic abnormalities, it would be preferable to discover that excess in the laboratory rather than at the time of amniocentesis or birth. Short argues that such a controlled *in vitro* study would also provide information concerning the probable success rate of *in vitro* fertilization.[8]

Several objections can be raised to such a proposal, as Short himself observes. First, there would be little basis for comparison following such a laboratory study since data concerning the incidence of abnormalities, particularly chromosomal abnormalities, in early human embryos following *in vivo* fertilization are quite limited. In fact, the totality of *in vivo* information relating to human preimplantation ova and embryos is "confined to 15 specimens, 9 recovered from the oviduct and 6 from the uterus."[9] At least two replies to this objection can be made. First, James Schlesselman notes that one can extrapolate statistically from three major studies of the incidence of chromosomal abnormalities following *in vivo* fertilization[10] that the natural incidence of such abnormalities in humans is between 396 per 1,000 and 477 per 1,000 at the time of implantation; prior to implantation the incidence of such abnormalities is presumably somewhat higher.[11] Schlesselman concludes

that a 40-50% chromosomal abnormality rate in human embryos following *in vivo* fertilization is a reasonable baseline against which to compare the results of *in vitro* fertilization. A second reply is proposed by Short himself, who suggests that one could perform a controlled study of the actual incidence of embryonic defects following *in vivo* fertilization by flushing early embryos from the reproductive tracts of consenting volunteer research subjects. Short concedes that this aspect of the proposed risk-assessment study would present both medical and ethical difficulties of its own.[12]

A second possible objection to Short's proposal for a laboratory risk-assessment study is that it is unnecessary. This objection can take one of two forms. Schlesselman notes that for every 1,000 chromosomal abnormalities which are present in implanted blastocysts, only 5 to 7 survive to the point of live birth. Thus, 99.3% to 99.5% of chromosomally abnormal fetuses are eliminated *in vivo* through spontaneous abortion or fetal death. It follows, therefore, that even a doubling in the incidence of chromosomal abnormalities following *in vitro* fertilization -- assuming that the technique or ancillary medical treatment did not facilitate the survival of abnormal embryos -- would yield only an additional 6 to 7 chromosomally abnormal fetuses, which could, in Schlesselman's view, be detected by means of prenatal diagnosis and selectively aborted.[13]

An alternative argument against the necessity of Short's proposed risk-assessment study can be based on the essays of Biggers, who asserts that for the investigation of most questions concerning human reproduction

a suitable animal model can be found. In his view, women should not be subjected to research risks and valuable human ova and embryos should not be used in research unless there is no reasonable alternative to a study in humans.[14]

Biggers' position suggests a final issue to be considered under the rubric of goals and potential benefits of the research: How stringent a standard should be set with respect to the need for laboratory research on human in vitro fertilization and embryo transfer? There are three possible answers to this question. The least stringent standard would be that benefits can be expected from the human research. A somewhat more stringent standard would be that human research should hold out the prospect of more significant or more reliable benefits than research employing animal models.[15] The most stringent standard would require that the promised benefits of human research be achievable only through research using human gametes and early human embryos.

B. The Design of the Research

Biggers emphasizes that research on human in vitro fertilization and embryo culture, since it involves human volunteers, "should only be undertaken if efficiently designed experiments of adequate size are possible."[16] In his view, this stipulation may require that collaborative trials be conducted. Schlesselman's discussion of appropriate sample size for answering specific questions regarding human in vitro fertilization illustrates both the complexity of the design issue and the essential role of the biostatistician in helping to plan laboratory research with human gametes and embryos.[17]

C. The Consent of Sperm and Ovum Donors

Most discussion of the consent question for laboratory studies of in vitro fertilization has focused on the ovum donor. In most cases ova are harvested from women with intact ovaries by means of laparoscopy. The donation of ova may be associated with receiving hormones to induce superovulation and/or to mature the ova in vivo prior to harvest. In some cases ova are harvested at the same time that a tubal ligation is performed. There is unanimous agreement that the informed consent of ovum donors must be secured in advance of their participation as research subjects.[18] In addition, the particular vulnerability of infertility patients, who are dependent on the health professions for assistance in achieving pregnancy and who nonetheless may be asked to serve as ovum donors, has been noted in the literature on the consent question.[19]

Less thoroughly discussed are the issues of consent by semen donors and the use of ova excised from ovarian tissue removed for clinical reasons. Consent by semen donors might be particularly difficult to secure if semen were secured from a sperm bank rather than from a prospectively recruited donor. The view expressed in one published assessment of in vitro fertilization is that prior consent should be secured from all males whose sperm are to be used for in vitro fertilization.[20]

The harvesting of ova from excised ovarian tissue may prove to be inefficient from a purely practical standpoint unless hormone treatments are administered in advance of surgery. Prior consent to such hormone treatment would presumably be secured. However, even if ova were harvested

from such tissue, without the previous administration of hormone to the female patient, gradually evolving general standards with respect to the use of human tissues for research purposes[21] would seem to suggest the necessity for securing the patient's consent to the use of her ova in laboratory research.

D. The Status of the Early Human Embryo

Two primary objections to laboratory research with human *in vitro* fertilization and embryo culture have been raised. The first is that such research is incompatible with the respect that is due to early human embryos. The second is that the potential adverse consequences of the research outweigh the potential benefits. These two objections will be discussed in the present and the succeeding section of this chapter.

The shape of the embryonic status question differs somewhat in the laboratory research context and the clinical context. As Leon Kass points out, many human embryos which would be studied in the laboratory would have been created solely for research purposes.[22] The major alternative would be to perform laboratory studies on untransferred embryos remaining after the fertilization of multiple ova and the transfer of only one to the uterus. However, from a research design standpoint, total reliance on the use of untransferred embryos would seem to exclude research on the fertilization process and on the earliest stages of embryonic development.

At least three distinguishable answers to the embryonic-status question in the research context have been proposed. Kass himself, impressed by the continuities in embryonic and fetal development and by

the potential viability of the early human embryo if it is transferred at the proper time, argues (1) that embryos ought not be deliberately created for research purposes[23] and (2) that no invasive or manipulative research should be performed on already-existing human embryos.[24] Any other policy would, according to Kass, symbolize the belief that early human embryos are "things or mere stuff."[25]

A second position on the embryonic-status issue is presented by Charles Curran, who argues that:

> From my ethical perspective truly human life is present two to three weeks after conception or shortly after the implantation of the embryo. Hence experimentation after that time and attempts to culture embryos in vitro beyond this stage raise insurmountable ethical problems.[26]

However, even for research involving the earliest stages of embryonic life Curran asserts that "[t]he nature of the matter involved in the research calls for respect and economy avoiding unnecessary waste."[27]

A similar position is articulated by Clifford Grobstein who suggests that "human cells, tissues and organs that have no reasonable prospect of possessing or developing sentient awareness" are "human materials rather than human beings or persons." Grobstein notes that "there are established practices for dealing with and disposing of human materials, practices that take into account the special status they have, having originated as human."[28] Grobstein's position is characterized as being similar rather than identical to Curran's for two reasons. First, it is not clear that Curran would extend his principle of respect to include non-embryonic human organs, tissues, or cells. Second, the criterion of possessing a potential for sentience seems not

to be a part of Curran's position on embryonic status. Indeed, one could construe this criterion broadly to include all preimplantation embryos since, as Kass notes, they could be transferred, implanted, and develop to maturity; or one could interpret the criterion narrowly to exclude all preimplantation embryos since it is infeasible, given the current state of medical technology, to culture human embryos in vitro beyond the blastocyst stage.

A third position on embryonic status, represented by Samuel Gorovitz, adopts sentience (rather than the potential for sentience) as the primary criterion for determining the moral status of the human embryo or fetus. In Gorovitz's view:

> The status of the embryo is not equivalent to that of a person, a child, an infant, or a fetus -- at least a fetus from the point of development of the capacity for even primitive sentience.[29]

If by "primitive sentience" Gorovitz means the capacity to respond to sensory stimuli, then the transition from embyronic to fetal status (at the eighth week of gestation) or, at the latest, the tenth gestational week of fetal development would seem to mark the transition from non-protected to protected status.[30] In fact, however, Gorovitz notes that he would draw the line of acceptability somewhat conservatively, that is, "rather close to the point where cell differentiation begins, rather far from the capacity for independent survival."[31]

A possible reason for the multiplicity of viewpoints on the status of the human embryo is suggested by Gorovitz. In his view, questions like embryonic status or the appropriate criteria of death are not matters of fact which can be clarified through appropriate research

programs. Rather, these questions provide the occasion for individuals to make decisions and for societies to establish policies.[32] In contrast, while Kass does not directly address the fact/decision distinction, he clearly regards the discontinuity of fertilization and the continuity of the embryonic development which follows as factual considerations which lead ineluctably to certain moral conclusions.[33]

E. Potential Adverse Consequences of the Research

Concerns about adverse consequences of laboratory research with human in vitro fertilization and embryo culture have been focused in three areas: (1) the same types of research procedures that have been performed with nonhuman mammalian embryos may be performed with human embryos; (2) certain undesirable technological or clinical applications may arise from such research; and (3) the research may have a desensitizing or dehumanizing effect on investigators.

Kass outlines some of the scientific procedures which in his view are likely to be applied in the future to human embryos:

1. Culture beyond the blastocyst stage;
2. Formation of hybrids or chimeras (intra-specific and inter-specific);
3. Gene, chromosome, and plasmid insertion, excision, or alteration;
4. Nuclear transplantation or cloning; and
5. The freezing of embryos.[34]

Kass ventures this prediction because, in his view, the same arguments which can be advanced to justify, for example, the simpler and earlier procedures proposed by Pierre Soupart can without logical contradiction

be extended to the more ambitious and later procedures outlined above. Among these justifying principles are the following:

1. "It is desirable to learn as much as possible about the process of fertilization, growth, implantation, and differentiation of human embryos and about human gene expression and its control.

2. "It would be desirable to acquire improved techniques for enchancing conception and implantation, for preventing conception and implantation, for the treatment of genetic and chromosomal abnormalities, etc.

3. "Finally, only research using human embryos can answer these questions and provide these techniques.

4. "There should be no censorship or limitation of scientific inquiry or research."[35]

Without specifically advocating the types of experiments which Kass regards as undesirable, Gorovitz adopts a general position which could in principle allow him to approve such experiments. If one extrapolates from Gorovitz's views on embryonic status, one concludes that he would approve any type of research procedure on the human embryo, provided only that the research terminated prior to the onset of embryonic or fetal sentience and that other canons of research ethics (consent of gamete donors, appropriate research design, etc.) were carefully followed.[36] Gorovitz explicitly accepts Kass's formal point that the justifying arguments for such research should be carefully formulated, in order to avoid the "slippery slope."[37] However, his material principle of drawing the dividing line at the point of sentience rather than fertilization or implantation seems, at least, to lead Gorovitz to approve as potentially beneficial the experiments which Kass regards as negative consequences of laboratory research with preimplantation embryos.

A specific research technique, interspecies fertilization using human sperm or ova, has provoked considerable discussion and therefore merits brief further comment. Cross-fertilization raises both conceptual and ethical questions. Conceptually, is fertilization research involving the use of only human sperm or human ova and the culture of the resultant hybrid embryo human research? Ethically, Kass regards such research as an adverse consequence of intraspecific in vitro fertilization. On the other hand, Short, while acknowledging that interspecific fertilization carries with it undertones of a novel type of genetic manipulation,[38] argues that technical and ethical hedges could be constructed to prevent what he regards as the major potential adverse consequence of such research -- namely, any effort to transfer the hybrid embryo into the uterus of a human or animal female for further development.

A second type of potential adverse consequence identified by some critics of human in vitro fertilization and embryo culture concerns possible applications of the research rather than the research procedures themselves. Kass suggests that the research might lead to the banking of human ova or embryos for commercial purposes.[39] In the literature on this topic several other potential adverse consequences are noted: the cloning of human beings, the creation of human/animal hybrids, and the development of devices which would allow for the extracorporeal gestation, or ectogenesis, of human embryos and fetuses.[40] Without commenting specifically on these potential developments, Gorovitz expresses reservations about the wedge argument in its predictive (as distinguished from its logical) form. He also expresses confidence in the collective capacity of human beings to exercise good judgment, citing as examples

public policy on abortion, appropriate treatment of newborn infants, the treatment of irretrievably comatose patients, and the setting of limits on the freedom of scientific inquiry.[41]

In an earlier essay on in vitro fertilization and cloning Leon Kass identified a third general type of potential adverse consequence which might result from laboratory research involving human embryos. According to Kass, one should "be concerned about the effects on the attitude toward and respect for human life engendered in persons who are engaged in such practices."[42] No other author has commented on the possibly dehumanizing effects on the researcher of human in vitro fertilization and embryo culture. It is probable that authors like Curran and Gorovitz would link the dehumanization question to the issue of embryonic or fetal status, arguing that only research on embryos which have developed beyond the two-to-three-week stage (Curran) or to the point of sentience (Gorovitz) would show disrespect for the human embryo or fetus and that only research which manifested such disrespect would be likely to desensitize the researcher.

FOOTNOTES

1. Short, R.V., Human In Vitro Fertilization and Embryo Transfer, a paper prepared for the Ethics Advisory Board, 1978, pp. 2-3; Mastroianni, Luigi, Jr., In Vitro Fertilization and Embryo Transfer, a paper prepared for the Ethics Advisory Board, 1978, p. 5.

2. Short, op. cit., pp. 3-5; Mastroianni, op. cit., p. 5.

3. Short, op. cit., pp. 5-6.

4. Mastroianni, op. cit., p. 5.

5. Ibid.

6. Ibid.

7. Short, op. cit., pp. 6-7.

8. Ibid., pp. 8-10.

9. Schlesselman, James J., How Does One Assess the Risk of Abnormalities From Human In Vitro Fertilization?, a paper prepared for the Ethics Advisory Board, 1979, p. 17; cf. Biggers, John D., In Vitro Fertilization, Embryo Culture and Embryo Transfer in the Human, a paper prepared for the Ethics Advisory Board, 1978, p. 6 and Appendix I, Table 3.

10. Schlesselman, op. cit., pp. 7-8, citing, Boue, J.G. and Boue, A., Chromosomal Anomalies in Early Spontaneous Abortion, Current Topics in Pathology, vol. 62, 1976, pp. 193-208; Creasy, M.R., Crolla, J.A., and Alberman, E.D., A Cytogenetic Study of Human Spontaneous Abortions Using Banding Techniques, Humangenetik, vol. 31, 1976, pp. 177-196; Alberman, E.D. and Creasy, M.R., Frequency of Chromosomal Abnormalities in Miscarriages and Perinatal Deaths, Journal of Medical Genetics, vol. 14, 1977, pp. 313-315.

11. Schlesselman, op. cit., p. 19.

12. Short, op. cit., p. 10; cf. Schlesselman, op. cit., pp. 24-25.

13. Schlesselman, op. cit., p. 30.

14. Biggers, op. cit., p. 412; cf. Kass, Leon R., Ethical Issues in Human In Vitro Fertilization, Embryo Culture and Research, and Embryo Transfer, a paper prepared for the Ethics Advisory Board, 1978, p. 27.

15. Walters, LeRoy, Ethical Issues in Human In Vitro Fertilization and Research Involving Early Human Embryos, a paper prepared for the Ethics Advisory Board, 1978, fn. 178, citing Mastroianni, Luigi, Jr., In Vitro Fertilization, in: Reich, Warren, ed., Encyclopedia of Bioethics, (vol. 4), New York, Free Press-Macmillan, 1978, pp. 1448-1451.

16. Biggers, op. cit., p. 41a.

17. Schlesselman, op. cit., pp. 20-27.

18. Short, op. cit., p. 9; cf. Walters, op. cit., pp. 37-38.

19. Walters, op. cit., fn. 182, citing National Research Council, Assembly of Behavioral and Social Sciences, Committee on the Life Sciences and Social Policy, Assessing Biomedical Technologies: An Inquiry into the Nature of the Process, Washington, D.C., National Academy of Sciences, 1975, p. 27.

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22. Kass, op. cit., fn. 14, p. 28.

23. Ibid., p. 5.

24. Ibid., pp. 10-11.

25. Ibid., p. 11.

26. Curran, Charles E., In Vitro Fertilization and Embryo Transfer: From a Perspective of Moral Theology, a paper prepared for the Ethics Advisory Board, 1978, p. 22.

27. Ibid., p. 26.

28. Grobstein, Clifford, Statement to the Ethics Advisory Board, Transcript of Meeting III, September 15, 1978, National Technical Information Service, PB-288 764, p. 229.

29. Gorovitz, Samuel, In Vitro Fertilization: Sense and Nonsense, a paper prepared for The Ethics Advisory Board, 1979, p. 28.

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31. Gorovitz, op. cit., p. 28.

32. Ibid., pp. 1-4.

33. Kass, op. cit., pp. 5-7.

34. Ibid., pp. 18-19.

35. Ibid., p. 20.

36. Gorovitz, op. cit., pp. 27-28.

37. Ibid., p. 15.

38. Short, op. cit., p. 7.

39. Kass, op. cit., p. 19.

40. Walters, op. cit., pp. 39-40.

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CHAPTER III: CLINICAL APPLICATIONS OF *IN VITRO* FERTILIZATION AND/OR EMBRYO TRANSFER: TECHNICAL AND ETHICAL ISSUES

A. The Need for and Potential Benefits of In Vitro Fertilization and Embryo Transfer

The major potential benefit to be derived from clinical applications of *in vitro* fertilization and embryo transfer is that it may enable some otherwise-infertile women to conceive and bear children. Most commentators on the clinical use of *in vitro* fertilization and embryo transfer view the alleviation of infertility, particularly in the context of heterosexual marriage, as a desirable goal.[1] In opposition to this majority position, however, Stanley Hauerwas argues that even within marriage, resort to *in vitro* fertilization as a method to overcome infertility reflects an undue emphasis on the importance of biological parentage.[2]

There are at least two senses in which the *need* for this potential benefit has been discussed. First, how many women who wish to bear children are infertile because of blocked Fallopian tubes? Second, of these infertile women, how many need *in vitro* fertilization and embryo transfer in the sense that they have no alternative means for producing children of their own?

Precise data on the extent of need in these two senses are unavailable. Rough estimates of the upper limits of need in the United States are provided by Biggers:

> There are 60 million women reproductively active in the USA; seven percent of couples are infertile, and a third of these are infertile because of sterility of the wife. Thus, there are 1,400,000 sterile women in the population. Pathology of the oviduct accounts for 40 percent of the cases so that there are about 560,000 women with diseased oviducts.[3]

The major alternative to in vitro fertilization and embryo transfer for women is one of several surgical procedures available for repairing blocked oviducts: salpingolysis, resection and reanastomosis, fimbrioplasty, and tubal implantation. According to a recent survey, the rates of term pregnancy following the first three of these procedures are 40-50%, 25-40%, and 10-25% respectively.[4] Thus, at least 280,000 U.S. women with tubal obstruction are not likely to achieve pregnancy by surgical methods alone. Of these women, an unknown number may also suffer from ovarian and/or uterine dysfunction and thus may be incapable of producing offspring even with the aid of in vitro fertilization and embryo transfer.[5] An additional adjustment in the estimate of the "need" for in vitro fertilization would be required if one were to consider women who had previously elected sterilization by tubal ligation but who later desire to become pregnant.

While the alleviation of infertility among couples is generally regarded as the major potential benefit of clinical in vitro fertilization and embryo transfer, some witnesses and some commentators in the literature have identified what they regard as additional benefits. Sid Leiman regards the surrogate-motherhood role as closely analogous to that of a wet nurse and therefore sees no ethical objection to extramarital involvement in gestation in cases in which intramarital reproduction is physically impossible.[6] In his writings on this topic R.G. Edwards mentions sex preselection as an additional potential benefit of clinical in vitro fertilization and embryo transfer.[7] Other potential

benefits cited by various authors are pre-transfer screening for abnormalities,[8] re-transfer repair of defects,[9] and extracorporeal gestation.[10] The potential consequences enumerated in this paragraph are not universally judged to be beneficial, however, as Section F below illustrates.

B. The Need for and Adequacy of Prior Laboratory and Animal Research

Three major types of studies have been proposed as precursors to clinical applications of *in vitro* fertilization and embryo transfer: (1) laboratory research on human sperm, ova, and embryos without embryo transfer, as described in Chapter 2, Section A above; (2) feasibility and safety studies in non-primate species; and (3) feasibility and safety studies in primates. Reservations have been expressed by some witnesses about each of these types of preliminary research.

Laboratory research with human sperm, ova, and embryos has been advocated most vigorously by R.V. Short. Short presents four arguments for a risk-assessment program based on such laboratory studies:

1. It would be better to discover an increased incidence, of abnormal embryos and/or low success rate "in the test tube rather than in the long-suffering female patient."

2. Laboratory tests could establish whether fertilization errors leading to potentially malignant trophoblastic tumors occur with *in vitro* fertilization.

3. Although chromosomally abnormal fetuses could be detected by amniocentesis, the discovery of such an affected fetus would confront an infertile couple with an agonizing decision; perhaps the decision would be viewed as a choice between having a handicapped child and no child at all.

4. Laboratory tests could establish whether the lack of the natural screen against defective sperm which is provided by the female reproductive tract leads to an increase in the number of abnormal embryos produced *in vitro*.[11]

Four possible lines of objection to the type of risk-assessment study proposed by Short are suggested by the testimony of other witnesses. Biggers notes that large numbers of human ova would need to be collected and used in such studies in order to attain statistical signifcance and that the research would therefore involve a substantial number of women acting as donors.[12] Second, even if risk-assessment studies with human sperm, ova, and embryos were considered a necessary preliminary step, it can be argued that such studies would not be sufficient, since they would not detect the subtle types of mental or developmental deficits which might be discovered in a carefully conducted study of primates.[13] (As will be noted below, Short regards primate studies as too time-consuming.[14]) Third, in Biggers' view, there is already sufficient evidence from laboratory studies with rats, mice, and rabbits and from the use of embryo transfer in farm animals to justify the conclusion that in vitro fertilization and embryo transfer do not produce a significant increase in the number of abnormal offspring. On this view, the conduct of laboratory studies as proposed by Short is unnecessary.[15] A final type of objection to risk-assessment studies with human gametes and embryos can be derived from Schlesselman's essay -- namely, that the efficiency of the human female reproductive system in screening against chromosomally abnormal embryos is so high (99.3% to 99.5%) that proceeding directly to embryo transfer in humans would probably not lead to a significantly higher number of abnormal fetuses (presumably detected by amniocentesis) or handicapped offspring. According to Schlesselman,

the primary result of an increase in the number of embryonic chromosomal abnormalities would be an increased rate of spontaneous abortion.[16]

A second proposal is to perform feasibility and safety studies in non-primate species of laboratory animals, e.g., the mouse and the rabbit. Mastroianni, a proponent of prior studies in both primate and non-primate species, asserts that:

> ... Extensive work in the laboratory animal should be a necessary prerequisite before proceeding with clinical trials. Statistically valid proof in animals that present techniques predictably produce normal offspring has not as yet been presented. Successful uterine transfer of in vitro fertilized ova has been accomplished in only two laboratory species.[17]

Short's position is in part similar to that of Mastroianni. In his view, the results of research with laboratory animals "although somewhat inadequate, are on the whole encouraging. The high abnormality rate in the rat experiment [conducted by Toyoda and Chang[18]] was probably not due to the in vitro procedure at all (Chang, personal communication) but nevertheless the experiment should be repeated."[19]

Kass indicates his agreement with the "cautious" position of Luigi Mastroianni, Benjamin Brackett, and R.V. Short that:

> ... The risks for humans have not been sufficiently assessed, in large part because the risks in animals have been so poorly assessed (due to the small number of such births and to the absence of any prospective study to identify and evaluate deviations from the norm).[20]

Two objections have been raised regarding studies with non-primate laboratory animals. First, Barton Childs observes that most animal species are so inbred that it would be invalid to extrapolate from the results of in vitro fertilization studies, even in large numbers of

laboratory animals, to the probable result of clinical applications in humans, who are outbred.[21] Second, in Biggers' view the results of studies with various laboratory animals and of the use of the procedures in farm animals already provide sufficient evidence of safety.[22]

A third possible objection to further studies with non-primate animals is implicit in the Sackett proposal: subtle mental deficits caused by in vitro fertilization might not be detected in non-primate animals.[23] Fourth and finally, Schlesselman's calculations concerning the low probability of producing abnormal human offspring following in vitro fertilization and embryo transfer[24] can be viewed as an argument against performing further risk-assessment studies with laboratory animals.

A third proposal for preliminary risk-assessment studies is advanced by Sackett. He recommends the conduct of a two-year trial in the pigtail monkey which would include (1) in vitro fertilization with some embryos transferred back to the donors of the ova and some transferred to other females, (2) a study of the incidence of abnormalities in products of in vitro fertilization, and (3) an assessment of learning abilities and development in the offspring of in vitro fertilization.[25] Gould advocates the use of another primate model, the squirrel monkey, for risk-assessment studies.[26]

Several objections have been or can be lodged against the proposal to perform primate risk-assessment studies. Short comments on the time-investment required:

> Whilst it would be helpful to have primate data, the constraints inherent in studying this problem in primates mean that it would be several years before adequate information would be forthcoming, and it would seem wrong to hold up progress until the information was available.[27]

Childs echoes this objection.[28] Second, as noted above, Childs argues that all non-human species are relatively or strictly inbred, so that the range of genetic variability present in humans cannot be duplicated in non-human species.[29] Two other general objections are also applicable to proposed primate research: (1) the studies already performed in several non-primate species provide sufficient evidence concerning risks (Biggers[30]), and (2) abnormal human embryos resulting from in vitro techniques are likely to be spontaneously aborted (Schlesselman[31]).

In summary, there is a clear division of opinion within the scientific and ethical communities concerning the need for and adequacy of prior laboratory and animal research. The extent of the disagreement is unclear because not all of the expert witnesses have discussed the three alternative risk-assessment strategies outlined above. In particular, few experts have had the opportunity to comment specifically on the Short and Sackett proposals.

The following positions, however, have been stated with clarity. Biggers regards further risk-assessment studies of any kind as unnecessary. Childs, while acknowledging the reassurance that further animal studies might provide, argues that such studies could never provide conclusive evidence. Short, Mastroianni, Kass, Sackett, and Gould agree that further risk-assessment studies should be performed but disagree on what kind of studies would be most feasible and appropriate. Short advocates the performance of in vitro studies with human sperm and ova and the replication of a single rat study; he opposes primate studies on grounds of infeasibility and the amount of time required. Mastroianni and Kass support the performance of additional studies in animals,

presumably in both primates and non-primates. Sackett and Gould regard non-primate risk-assessment studies as insufficient for drawing conclusions concerning primates and therefore recommend the conduct of primate research. In a word, there is majority support among the expert witnesses for some type of additional risk-assessment study but only minority support for any particular kind of study.

In addition, the data and calculations presented by Schlesselman may be relevant to the entire risk-assessment question. Schlesselman's thesis, which has not been commented on by proponents of risk-assessment studies, is that the probability of producing chromosomally-abnormal infants by means of clinical applications of in vitro fertilization and embryo transfer is quite low because of the human female's highly-efficient natural screen against chromosomally-abnormal embryos.

A little-discussed aspect of the risk-assessment debate is the kind of model (regarding proof of safety) which the protagonists have in mind. This model, in turn, can have important implications for the burden of proof issue. If one accepts the drug-testing model, as Short does, then the burden of proof is on investigators to demonstrate that the techniques of in vitro fertilization and embryo transfer are safe.[32] (It should be noted that, in a published essay, R.G. Edwards accepts the drug-testing model but argues that the results to date in several species of non-primate laboratory animals constitute sufficient proof of safety.[33]) On the other hand, if one adopts a surgery model, as Gorovitz does, than one can argue that the clinician is free to adopt new techniques unless opponents can demonstrate that prohibition of the techniques is justified.[34]

C. Risks of Procedures

1. Risks to Potential Offspring

The major sources of potential risk to offspring from in vitro fertilization and embryo transfer have been briefly outlined in Chapter 1, Section B.[35] In general, the surgical procedure of embryo transfer seems to occasion the least concern, in part perhaps because of the widespread use of embryo transfer following natural fertilization in farm animals.[36] The conditions under which the early embryo is cultured are also not a matter of primary concern, since the early mammalian embryo is known to be highly resistant to damage from environmental insults.[37] The major potential sources of damage to the early embryo are related to either the development of ova, the selection of sperm, the fertilization process, or the freezing of gametes or embryos. Specifically, potential sources of damage are the following:

a. Superovulation, sometimes employed prior to in vitro fertilization, may be correlated with an increase in the incidence of a chromosomal abnormality (trisomy) in embryos.[38]

b. The quality of sperm reaching and fertilizing the ovum in vitro may differ from the quality of sperm fertilizing the ovum in the Fallopian tube, since the female reproductive tract selects against some types of abnormal sperm.[39]

c. The quantity of sperm reaching the ovum simultaneously in vitro may break down the usual block to fertilization by multiple sperm; a polyploid embryo may result.[40]

d. The use of freezing techniques to preserve gametes or embryos may produce mutations.[41]

The precise extent to which each of these theoretical sources of risk is likely to be realized in human clinical applications of in vitro

fertilization and embryo transfer cannot be estimated with certainty. The data and calculations of Schlesselman suggest that even if an excess of chromosomally abnormal embryos were produced by in vitro techniques, only a small proportion (less than 10%) would develop to term because of the natural process by which most such embryos are lost early in gestation. Whether the ancillary medical treatment associated with in vitro fertilization and embryo transfer would enhance the survivability of chromosomally abnormal embryos is unknown, as Schlesselman acknowledges.[42] Similarly, if subtler genetic (as distinguished from chromosomal) abnormalities were to result from in vitro techniques, the abnormal embryos might not be affected by the natural screening process described by Schlesselman.

Judgments about the acceptability of various levels of risk to offspring diverge. Kass would require that such risks be equivalent to or less than those of natural reproduction.[43] Curran adopts a similar (although perhaps slightly less stringent) position, arguing that the risks of the in vitro fertilization and transfer procedures to the offspring ought to be "about the same as in the normal process."[44] On the other hand, Bigger notes that there is an estimated three percent additional risk of abnormality in offspring suggested by animal studies, and suggests that such an added risk would be acceptable, particularly in light of the fact that some couples who receive genetic counseling are not deterred from procreation by a twenty-five percent risk of genetically-abnormal offspring.[45]

Schlesselman explicitly raises the question: to what are the risks of human in vitro fertilization being compared? His answer is that the women and embryos being used for comparison should have the same medical history relevant to their infertility as those undergoing in vitro fertilization and embryo transfer.

2. Risks to donors

Most discussion of risks to donors has focused on risks to the women donating ova. The following sources of risk have been identified:

a. Hormonal treatment of the women, sometimes employed to induce superovulation; this treatment can lead to ovarian hyperstimulation or ovarian cysts.[46]

b. Laparoscopy, a surgical procedure generally performed under general anesthesia; this procedure may have to be repeated.[47]

c. Ectopic pregnancy, a potential danger if the embryo fails to implant in the uterus.[48]

d. Careful monitoring of any resulting uterine pregnancy, often including amniocentesis.[49]

e. The possibility of a higher-than-average rate of embryo loss or spontaneous abortion.[50]

These risks are considered to be comparable to the risks faced by female infertility patients, in general, and by women who undergo surgery for the correction of blocked Fallopian tubes, in particular.[51]

D. The Consent of Sperm and Ovum Donors

The issue of informed consent by sperm and oocyte donors was not addressed by the expert witnesses who testified before the Board. In the literature, however, there is unanimous agreement that the informed consent of the would-be mother and presumably of both parents must be secured. Several specific items of information have been identified by various commentators as being material to the decision of the couple and therefore requiring disclosure:

a. The availability of potentially effective alternative therapies, e.g., surgical reconstruction of the Fallopian tubes.[52]

b. The anticipated need for repeated laparoscopies.

c. The low probability of success.

d. The likelihood that the primary beneficiaries of the research will be other couples rather than the research participants themselves.[53]

e. The sources of the gametes to be used in the attempted in vitro fertilization (i.e., a guarantee that only the sperm and ova of the couple will be employed).[54]

f. The disposition to be made of sperm, ova, and embryos not used in the transfer attempt.[55]

In the literature on informed consent, several commentators have remarked that infertility patients may be strongly influenced by their desperate desire to have children.[56] On the other hand, R.G. Edwards notes that many candidates for in vitro fertilization and embryo transfer are professional persons or their wives. Edwards expresses confidence that the patients seeking this therapy are fully capable of understanding and consenting to its procedures.[57]

E. The Status of the Early Human Embryo

The question of embryonic status in the clinical context differs to some extent from the same question in the laboratory-research context. Perhaps the most obvious difference is that in the clinical context there is at least a possibility that each embryo "created" will be transferred to the uterus, will implant, and will develop to the point of viability. Because of this difference in probabilities, as well as the directly-therapeutic intention present in the clinical context, most expert witnesses on ethical issues surrounding in vitro fertilization and embryo transfer viewed the status of the early embryo as less problematic in the clinical situation.

For persons who regard the embryo as deserving of respect or protection from the time of fertilization there are two major concerns: (1) loss of embryos following transfer, and (2) the disposition of untransferred embryos. Kass argues that there is no qualitative difference between embryonic loss following natural reproduction and that which follows *in vitro* fertilization.[58] The second issue is somewhat more complex, however, since, as Kass notes, the "surplus" embryos can be transferred to women other than the donor, used for laboratory research purposes, or allowed to die.[59] A fourth possibility, not mentioned by Kass, would be to freeze the untransferred embryos, perhaps for later transfer to the same donor. Among the first three possibilities, Kass expresses a clear preference for allowing untransferred embryos to die. In his view, this choice is most compatible with concerns about lineage (which would argue against transfer to other women) and about the respect which is owed to early human embryos.[60] Curran's position on the discard of embryos is similar to that of Kass, although Curran adds the note that discards and losses should be minimized insofar as possible.[61]

A potential method for reducing the number of untransferred embryos is suggested by both Kass and Leiman[62]: ova could be fertilized one at a time, and any additional ova could be stored, perhaps by freezing, for future attempts at *in vitro* fertilization and embryo transfer. A possible objection to this one-at-a-time procedure is that if fertilization failed to occur, embryo transfer might be delayed until the next menstrual cycle.

An issue not discussed by the expert witnesses and only hinted at in the literature on in vitro fertilization is the disposition of grossly abnormal embryos. Some have argued that to decide that such embryos should not be transferred is the first step toward deciding which fetuses (or persons) are not worthy to live.

Finally, some witnesses such as Gorovitz and Short do not explicitly consider the issue of embryonic status in the clinical context. However, if one extrapolates from their views on embryonic status in general or on laboratory research with early embryos, one can conclude with some confidence that they would regard the embryonic loss following embryo transfer and the discard of untransferred embryos as ethically acceptable.

F. Potential Adverse Consequences of Clinical Applications

Two types of potential adverse consequences of in vitro fertilization and embryo transfer have been identified: (1) adverse consequences for the family; and (2) other adverse consequences. Kass notes that even if the initial aim of clinical applications is to assist married couples to bear children of their own, the techniques employed provide "the immediate possibility" of egg donation (egg from donor, sperm from husband), embryo donation (egg and sperm both from outside the marriage), and foster pregnancy (another woman carrying the pregnancy to term).[63] In Kass's view, there will be a strong demand for such extramarital uses of the clinical procedures -- a demand which, if fulfilled, will further compromise "the virtues of family, lineage, and heterosexuality" or weaken "the taboos against adultery and even incest."[64]

Responses to the thesis that clinical uses of in vitro fertilization and embryo transfer will weaken the family have taken two forms. The first, represented by Gorovitz, is to argue that the demand for laboratory-assisted methods of reproduction in general will be limited and that other technological innovations (e.g., modern contraceptive techniques) will have a much more significant adverse impact on the family.[65] A second kind of response, briefly developed by Leiman, is to deny that surrogate motherhood is necessarily detrimental to the family, if this novel method of becoming a parent is resorted to for good reasons (e.g., if a couple would otherwise be unable to have a child).[66]

Other potential consequences considered adverse by some expert witnesses and commentators include:

a. The development of commercial ovum and embryo banks.[67]

b. The genetic selection or manipulation of early embryos.[68]

c. The transfer of nuclei from adult individuals to early embryos, or cloning.[69]

d. Extracorporeal gestation, or bringing an embryo all the way to viability in the laboratory.[70]

As noted above in Section A of the present chapter, the second and fourth consequences in this list are regarded by some commentators as potential benefits of clinical in vitro fertilization and embryo transfer. Few have advocated that commercial ovum and embryo banks be created or that human beings be cloned. Some commentators (for example, Gorovitz) have advanced the procedural suggestion that each potential consequence of in vitro fertilization and embryo transfer be carefully evaluated from the standpoint of both likelihood and probable impact.[71]

G. Questions of Allocation

Three general positions on the allocation issue can be distinguished. The first, represented by Biggers, is that applied laboratory research directed toward improving techniques for testing infertility by means of in vitro fertilization and embryo transfer should receive high priority -- or, at least, that it should receive a higher priority than basic laboratory research involving human gametes and embryos. The primary rationale for this position is Biggers' view that the supply of human ova available for research purposes is extremely limited and should be devoted either to directly clinical purposes or to answering questions that cannot be satisfactorily resolved by studying laboratory animal.[72]

A second position, represented by Leiman[73] and Curran[74], is that the federal government should support the clinical application of in vitro fertilization and embryo transfer. Leiman regards involuntary infertility as an extremely serious problem.

> The rabbis put it this way, some fifteen centuries ago. Four are considered as if they were dead: the poor, the diseased, the blind, and the childless.[75]

In his view, the public funding of medical means for overcoming infertility (for example, through Medicaid) is entirely appropriate. Indeed, Leiman argues that:

> It would be a sad commentary on the American ethos if federal funds could be used for the taking of human life, that is, therapeutic abortion, but not the creation of human life, that is, therapeutic conception.[76]

Although Kass disagrees with this second position, he presents an additional argument which some have used to support it:

> ... As he who pays the piper calls the tune, Federal support would make easy the Federal regulation and supervision of this research.[77]

In contrast, a third position on allocation is that federal funds should not be spent for in vitro fertilization and embryo transfer in clinical practice. Hauerwas, Gorovitz, and Kass all take this position, although for somewhat different reasons. In Hauerwas' view, the importance of being pregnant or of bearing a child that is genetically "one's own" has been overstated. Therefore the substantial investment of public funds to develop these anti-infertility techniques, particularly in light of other "immense needs of our society," (for example, the provision of an effective clotting factor for hemophiliacs) is inappropriate.[78] While he may not share Hauerwas' views on parenthood, Gorovitz agrees with his sense of priorities.

> In the competition for support, the burden of making a convincing case should rest with the proponent of a given line of work. With forty million Americans having no adequate access to decent health care, with thousands of children born annually without prospect of a family to nurture them, with venereal disease -- a major cause of infertility -- on the rise, it is implausible that research into making IVF more readily and reliably available should be a project of high priority concern. It isn't so much the harm or risk it involves as the plainly greater importance of addressing more fundamental and widespread problems of health and the delivery of health care.[79]

Kass presents three arguments for assigning a low priority to clinical applications of in vitro fertilization and embryo transfer. First, in agreement with Hauerwas and Gorovitz, he asserts that other

health-related needs are more pressing. Kass goes on to argue that even within the sphere of infertility research, other approaches will be more cost-effective:

> ... With money for research as limited as it is, research funds targeted for the relief of infertility should certainly go first to epidemiological and preventive measure -- especially where the costs of success in the high-technology cure are likely to be great.[80]

Second, according to Kass, the non-financial costs of developing these technologies -- that is, their potential adverse consequences -- also militate against assigning their development a high priority.[81] Finally, Kass notes that a substantial number of American citizens are opposed on moral grounds to research on, or application of, in vitro fertilization in humans. In his view, these citizens would strenuously -- and legitimately -- object to any use of their taxes to promote human in vitro fertilization and embryo transfer.[82]

FOOTNOTES

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3. Biggers, John D., In Vitro Fertilization, Embryo Culture and Embryo Transfer in the Human, a paper prepared for the Ethics Advisory Board, 1978, p. 35.

4. Biggers, op. cit., p. 36 and Table 4, p. 37, citing Shane, J.M., Schiff, I., and Wilson, E.A., The Infertile Couple, Clinical Symposia, vol. 28, 1976, pp. 1-40.

5. Biggers, op. cit., p. 35; Kass, op. cit., pp. 36-37.

6. Leiman, op. cit., pp. 126-130.

7. Walters, LeRoy, Ethical Issues in Human In Vitro Fertilization and Research Involving Early Human Embryos, a paper prepared for the Ethics Advisory Board, 1978, fn. 112, citing Edwards, R.G., Fertilization of Human Eggs In Vitro: Morals, Ethics, and the Law, Quarterly Review of Biology, vol. 49, 1974, p. 12.

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13. Sackett, Gene P., A Nonhuman Primate Model of Developmental Risk Following In Vitro Fertilization and Embryo Transfer, a paper prepared for the Ethics Advisory Board, 1979, pp. 26-28.

14. Short, op. cit., p. 8.

15. Biggers, Statement to the Ethics Advisory Board, op. cit., pp. 257, 260-261.

16. Schlesselman, James J., How Does One Assess the Risk of Abnormalities from Human In Vitro Fertilization?, a paper prepared for the Ethics Advisory Board, 1979, pp. 29-31.

17. Mastroianni, Luigi, Jr., In Vitro Fertilization and Embryo Transfer, a paper prepared for the Ethics Advisory Board, 1978, p. 6.

18. Toyoda, Y. and Chang, M.C., Fertilization of Rat Eggs In Vitro by Epididymal Sperm and the Development of Eggs Following Transfer, Journal of Reproduction and Fertility, vol. 36, 1976, pp. 9-22.

19. Short, op. cit., p. 8.

20. Kass, op. cit., 1978, pp. 12-13.

21. Childs, Barton, Statement to the Ethics Advisory Board, Transcript of Meeting III, September 16, 1978, National Technical Information Service, PB-288 764, pp. 252-253.

22. Biggers, Statement to the Ethics Advisory Board, op. cit., pp. 257, 260-261.

23. Sackett, op. cit., pp. 26-28.

24. Schlesselman, op. cit., pp. 29-31.

25. Sackett, op. cit., pp. 31-32.

26. Gould, Kenneth G., Fertilization In Vitro of Nonhuman Primate Ova: Present Status and Rationale for Further Development of the Technique, a paper prepared for the Ethics Advisory Board, 1978, pp. 21-23.

27. Short, op. cit., p. 8.

28. Childs, op. cit., p. 232a.

29. Ibid.

30. Biggers, Statement to the Ethics Advisory Board, op. cit., pp. 257, 260-261.

31. Schlesselman, op. cit., pp. 29-31.

32. Short, op. cit., pp. 8-10.

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44. Curran, Charles E., In Vitro Fertilization and Embryo Transfer: From a Perspective of Moral Theology, a paper prepared for the Ethics Advisory Board, 1978, p. 19.

45. Biggers, Statement to the Ethics Advisory Board, op. cit., pp. 261-263; see also Shulman, Joseph, Testimony for the Ethics Advisory Board, 1978, p. 3.

46. Gould, op. cit., p. 17; Mastroianni, op. cit., p. 3.

47. Gould, op. cit., pp. 17-18.

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52. Kass, Leon, Making Babies -- the New Biology and the 'Old' Morality, Public Interest, vol. 26, 1972, p. 31.

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58. Kass, op. cit., pp. 9-10.

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60. Ibid., pp. 9-11.

61. Curran, op. cit., pp. 17, 26.

62. Kass, op. cit., 1972, p. 34; Leiman, op. cit., p. 126.

63. Kass, op. cit., 1978, p. 15.

64. Ibid.

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66. Leiman, op. cit., pp. 128-129.

67. Kass, op. cit., 1978, p. 19.

68. Walters, op. cit., fn. 113 (see fn. 9 above).

69. Ibid.

70. Ibid, fn. 118 (see fn. 10 above).

71. Gorovitz, op. cit., pp. 14-15.

72. Biggers, Statement to the Ethics Advisory Board, op. cit., pp. 236-237.

73. Leiman, op. cit., pp. 130-131.

74. Curran, op. cit., p. 28.

75. Leiman, op. cit., p. 131.

76. Ibid.

77. Kass, op. cit., 1978, p. 22.

78. Hauerwas, op. cit., p. 18.

79. Gorovitz, op. cit., p. 26.

80. Kass, op. cit., 1978, p. 25.

81. Ibid.

82. Ibid., pp. 28-29.

CHAPTER IV: LEGAL ISSUES SURROUNDING HUMAN IN VITRO FERTILIZATION, EMBRYO CULTURE, AND EMBRYO TRANSFER

Two papers written for the Board examined the legal issues surrounding human in vitro fertilization; one was prepared by Dennis Flannery and his colleagues at the Washington law firm of Wilmer, Cutler and Pickering, the other was written by Barbara Katz, Office of Legal Affairs, University of Colorado Medical Center. The discussion which follows reflects the legal analysis and conclusions presented by the two papers; in any areas where they differed, the differences are noted. Four main topics are addressed: (A) existing law that might be applicable to human in vitro fertilization and embryo transfer; (B) Constitutional questions raised either by the use, or by restrictions imposed on the use, of the techniques; (C) possible implications for tort liability; and (D) criminal law.

A. Existing Federal and State Law Applicable to Human In Vitro Fertilization and/or Embryo Transfer

1. Federal Law

The only existing federal control of human in vitro fertilization is a regulation of the Department of Health, Education, and Welfare:

> No application or proposal involving human in vitro fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.[1]

In its notice of proposed rulemaking entitled "Protection of Human Subjects: Proposed Policy" issued August 23, 1974, the Department indicated the kind of issues it expected the Ethics Advisory Board to consider:

> With respect to the fertilization of human ova in vitro, it is expected that the Board will consider the extent to which current technology permits the continued development of such ova, as well as the legal and ethical issues surrounding the initiation and disposition of such products of research.
>
> With respect to implantation of fertilized human ova, it is expected that the Board will consider such factors as the safety of the technique (with respect to offspring) as demonstrated in animal studies and clarification of the legal responsibilities of the donor and recipient parent(s) as well as the research personnel.[2]

Two other general requirements of HEW regulations are presumably applicable to research involving human in vitro fertilization, as well. All such research conducted or supported by the Department must be reviewed by a local Institutional Review Board (IRB)[3]; in addition, studies involving human in vitro fertilization should not be conducted or supported by HEW unless "appropriate studies on animals and nonpregnant individuals have been completed."[4]

Moreover, the Department interprets the National Research Act as authorizing (if not requiring) IRB review of human research not funded by HEW at any institution which receives a grant or contract involving human subjects under the Public Health Service Act.

> The Secretary shall by regulation require that each entity which applies for a grant or contract under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant or contract assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an 'Institutional Review Board') to review biomedical and behavioral research involving human subjects conducted at or sponsored by such entity in order to protect the rights of the human subjects of such research.[5]

However, the standards to be employed by the local Institutional Review Board in reviewing non-federally funded human research are not specified by the statute.

2. State Law

No state has enacted legislation or promulgated regulations directly governing human in vitro fertilization and/or embryo transfer. Such laws or regulations could affect the conduct of research involving in vitro fertilization within particular jurisdictions, especially since the federal regulations governing such research specifically do not preempt state or local law in this sphere:

> Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.[6]

The types of existing law which provide the closest analogies to human in vitro fertilization and/or embryo transfer are state statutes or court decisions concerning (a) artificial insemination and (b) research involving human fetuses.

Within the context of family law, the issue of artificial insemination, especially artificial insemination with donor sperm (AID), has received legislative or judicial attention in approximately one-third of the states. Case law concerning AID has focused primary attention on whether AID is equivalent to adultery and thus, whether children conceived as a result of AID are legitimate. (Legitimacy has implications both for inheritance rights and for claims to paternal support.) The general trend of recent case law, particularly in California and New York, has

been toward the view that AID does not constitute adultery and that children conceived as a result of AID are legitimate.[7] Nineteen states have enacted legislation regarding one or more aspects of artificial insemination; many of the statutes include a requirement for prior written consent by both husband and wife.[8] However, in the remaining states, the legal status of children conceived following AID is left in doubt.

A second area of state legislative interest -- research with live human fetuses -- is also at least partially analogous to research involving human in vitro fertilization. Approximately sixteen states have enacted statutes governing fetal research. The primary focus of all such statutes is the permissibility of research on the fetus (1) following implantation and (2) before, during, or after induced abortion. However, the language of at least one state statute on fetal research may be sufficiently broad to encompass, as well, research involving unimplanted early human embryos.[9]

B. Constitutional Issues

1. Preliminary Distinctions

Federal or state action may be found unconstitutional if it infringes upon a fundamental right of United States citizens and the government cannot demonstrate (1) that the law is necessary to protect a "compelling state interest" and (2) that it does not go beyond what is necessary to protect those interests.[10] If, on the other hand, a governmental action restricts individual activities in ways that do not infringe a fundamental right, then the government need only show that its action is rationally related to a constitutionally permissible purpose.[11] Thus, a critical

question regarding human in vitro fertilization -- whether in the laboratory or the clinical context -- will be whether individuals proposing to employ, or seeking access to, the technique can be said to be asserting a fundamental legal right. This, in turn, determines whether the government will be required to justify its regulation of human in vitro fertilization by demonstrating a compelling state interest that it seeks to protect or only by demonstrating a rational basis for its action.

A second distinction is also important: the distinction between a governmental restriction of an activity, on the one hand, and a governmental decision not to fund the activity, on the other. In 1977, in a case challenging the constitutionality of restrictions on the use of Medicaid funds for abortions, the United States Supreme Court held that a governmental restriction of the use of public funds to support the exercise of a fundamental right does not, by itself, constitute impermissible interference with the exercise of that right.[12] The Court concluded that the existence of a fundamental right "implies no limitation on the authority of a state to make a value judgment [to discourage the exercise of that right] and to implement that judgment by the allocation of public funds."[13] As applied to the question of in vitro fertilization, that langauge suggests that a governmental decision to restrict either laboratory research or clinical applications of the technique would need stronger justification than would a decision not to provide funds for such activities.

2. Clinical Applications of In Vitro Fertilization and Embryo Transfer

Constitutional principles affecting reproductive activity are more fully articulated than those relating to basic laboratory research.

Therefore, it is useful to examine the rights pertaining to reproductive choices before attempting to analyze what rights might be implicated in government regulation of basic laboratory research.

The argument for a constitutional right to reproduce by means of in vitro fertilization would rest on the right to privacy as related to procreation, the marital relationship, and contraception. In 1942, in a decision striking down Oklahoma's compulsory sterilization law, the Supreme Court held that individuals have a right to be free from unwarranted governmental interference with procreative capabilities. (Skinner v. Oklahoma)[14] This might be termed "the right to procreation."[15] A second constitutionally protected area is the privacy of the marital relationship. This was recognized in a 1965 decision (Griswold v. Connecticut) invalidating a Connecticut statute forbidding the use of contraceptives by married couples. There, the Court said:

> The entire fabric of the Constitution and the purposes that clearly underlie its specific guarantees demonstrate that the rights to marital privacy and to marry and raise a family are of similar order and magnitude as the fundamental rights specifically protected . . . .The fact that no particular provision of the Constitution explicitly forbids the State from disrupting the traditional relation of the family -- a relation as old and as fundamental as our entire civilization -- surely does not show that the Government was meant to have the power to do so.[16]

The privacy interests recognized in Griswold were expanded in later cases to include "the right of the individual, married or single, to be free from governmental intrusion into matters so fundamentally affecting a person as the decision whether to bear or beget children."[17]

The extent to which any individual's access to in vitro fertilization will be viewed as involving a fundamental right will depend upon how closely analogous it is to the rights already recognized by the Supreme Court. Thus, for example, a married couple with no alternative means for having a child of their own could claim that restriction of access to in vitro fertilization is interference with the fundamental right of marital privacy and with their right to choose whether, and in what manner, to achieve procreation. Since these rights are reasonably analogous to those recognized by the Court in Skinner, Griswold, and Eisenstadt, the argument might well be persuasive. If the Court agreed with the view that the rights in this instance are fundamental, the government would have to demonstrate a compelling state interest to justify interfering with the exercise of those rights.

On the other hand, an unmarried woman who wished to utilize in vitro fertilization followed by embryo transfer to another (surrogate) mother, in order to have a genetic child of her own without the expense and inconvenience of pregnancy, would have a much weaker case. There would be neither marital privacy nor a procreative capacity, in the normal sense, to protect. Thus, courts might well find the right asserted to be less than fundamental, and the government would have to show only a rational basis for restricting the exercise of that "right".

Several grounds for prohibiting or limiting access to clinical applications of in vitro fertilization could be advanced. First, a state or the federal government might argue that this reproductive technique inevitably involves the loss of human embryos. Accordingly,

a government might enact legislation to protect early human embryos. Such a law might pass the rational basis test but might not withstand constitutional challenge by individuals who could assert a fundamental right to access to in vitro fertilization.[1]

A second possible basis for state intervention in the clinical applications of in vitro fertilization would be the government's interest in fostering marriage and discouraging illegitimacy. This rationale might be proffered, for example, in support of a law restricting publicly funded in vitro fertilization and embryo transfer to married couples.[19] There is little room for doubt that such a funding limitation would be found constitutionally permissible; it is not clear, however, whether courts would uphold an outright prohibition on the access of single persons to in vitro fertilization and embryo transfer.[20]

Third, a government might prohibit or limit access to clinical applications of in vitro fertilization in order to preclude institutional or individual genetic planning or manipulation. It has been suggested that the potential social impact of a large-scale genetic program might justify governmental regulation, but that interference with the genetic planning of individual families would have to be justified by a compelling state interest.[21]

Fourth, a state or the federal government might conclude that the use of surrogate or host mothers in connection with clinical in vitro fertilization would create insuperable legal problems that would

justify a prohibition of such activities -- perhaps on the ground that service as a surrogate mother is an unacceptable form of employment.[22] In the opinion of Flannery and associates such a prohibition would probably withstand legal challenge on both "rational basis" and "compelling state interest" grounds.[23]

Finally, if clinical applications of *in vitro* fertilization should appear to present health risks to mother or offspring which are substantially greater than those usually associated with conception and childbirth, then a state or the federal government might well decide to prohibit or limit access to this reproductive technique. Whether such a state intervention would withstand constitutional challenge would depend in part on the probability and magnitude of the risks involved.[24]

In addition to making basic decisions regarding the regulation of access to clinical applications of *in vitro* fertilization, the states and the federal government may wish to establish policies on such related matters as the legal status of children who are produced by means of *in vitro* fertilization and embryo transfer, the role of attending physicians in decisions regarding implantation and abortion, and record-keeping requirements.[25]

3. Laboratory Research Involving In Vitro Fertilization and/or Embryo Culture

a. Constitutional bases for asserting a right to perform or participate in laboratory research involving in vitro fertilization and/or embryo culture. Two major constitutional arguments could be advanced in support of basic laboratory research involving human *in vitro* fertilization. The first is freedom of inquiry, or the right

of scientists to perform their research without governmental interference. This argument can be asserted most vigorously in defense of research conducted without the assistance of government funding. The second is the right of individuals to dispose of their genetic material as they see fit.

In a recent report, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research expressed the view that although the Supreme Court might recognize a First Amendment right to seek new ideas or knowledge (i.e., a "right to research")[26], that must be distinguished from a right to be free from regulations governing the manner in which research may be conducted.[27]

> ... [T]he state may not interfere with the researcher's choice of the end or topic of research, but it may regulate only the methods used in the research, in order to protect interests in health, order and safety with which unrestricted research might conflict. Such restrictions are valid if they are reasonably related to protection of non-speech interests and are not so vague and over broad that they chill the exercise of protected speech.[28]

Accepting the National Commission's distinction between the goal and the manner of research as valid, then the applicability of this putative right to basic research involving human in vitro fertilization is problematic, since it is the manner of achieving the knowledge -- that is, through the creation and study of human embryos -- that is most likely to be the target of governmental regulation.[29]

A second constitutional argument in support of laboratory research involving human in vitro fertilization focuses attention on the rights of potential gamete donors to dispose of their reproductive cells in

whatever manner they see fit. According to this view, donors have a "constitutionally protected fundamental privacy right to control the use and manipulation of their own genetic materials."[30] Such a privacy right is clearer, however, in cases involving contraception or abortion than in the case of genetic materials donated for basic laboratory research. Once the materials are outside the body of the donor, any personal rights of privacy regarding their use become attenuated.[31]

b. Constitutional bases for governments' prohibiting or refusing to fund laboratory research involving human in vitro fertilization. If the analysis of the preceding section is accepted, then it would appear that no fundamental constitutional right to perform or participate in basic research involving in vitro fertilization is likely to be found. In the absence of such a right, the government could, if it wished, prohibit in vitro fertilization research if it had a rational basis for doing so. A prohibition would most probably be based on the view that the creation, study, and destruction of early human embryos is inconsistent with the dignity which should be accorded to forms of potential human life. Even if a fundamental right to conduct or participate in such research did exist, the government could still decline to support it with public funds. Such a refusal could be based on an administrative determination that other areas of research would be more useful to the government.[32]

If research with early human embryos were to involve embryo transfer and subsequent implantation, the current HEW regulations governing fetal research would apply, since the "fetus" is defined as the embryo "from the time of implantation."[33] State statutes regarding fetal research might or might not apply, depending on their formulation.

In addition to deciding whether to prohibit or to support laboratory research involving human in vitro fertilization, states or the federal government might wish to formulate standards governing the conduct of such research, if the research is permitted. For example, regulations to protect the health of ovum donors or to set standards for protecting the dignity of potential human life might be adopted. Moreover, a government might require that gamete donors consent in advance to the use of their reproductive cells in research involving in vitro fertilization. These procedural regulations, designed to achieve a rational governmental purpose, should be constitutionally permissible.[34]

C. Liability for Injuries

The federal government might be liable for injuries arising from in vitro fertilization in research programs conducted or supported by HEW. This section explores three questions: (1) whether such suits would be barred by the doctrine of sovereign immunity; (2) what causes of action might be considered valid; and (3) whether a program could be established to provide compensation for such injuries.

1. Sovereign immunity. Under the Federal Tort Claims Act, the United States is liable for the "negligent or wrongful" acts or omissions of its employees while they are acting within the scope of their employment.[35] Exceptions to such liability include acts or omissions that are within an agency or officer's "discretionary duty" (as, for example, a decision to initiate a particular research program).[36] Whether the doctrine of sovereign immunity would bar a suit for damages arising within an HEW-conducted or supported research program involving in vitro fertilization would depend upon:

1. Whether the investigator is considered a federal "employee." (Does this category include, for example, grantees or contractors in HEW-funded research programs?)

2. Whether the alledged wrong occurred because of the employee's exercise of protected "discretionary functions" at the policy level or through a failure to exercise due care in a particular program at the operational level.

3. Whether the employee's act fell within an exception to liability under the Federal Tort Claims Act.

The Board's legal consultants suggest that the United States, but not individual investigators, would probably be liable for any negligence of subordinate HEW officers or employees who design or conduct a particular research program involving in vitro fertilization. If the conduct violated existing HEW regulations, even the discretionary exception would not prevent liability.[37]

2. Possible causes of action

a. Actions on behalf of the child. Two kinds of suits might be brought on behalf of a child born alive with handicaps following in vitro fertilization and embryo transfer. First, a suit might be brought on the basis of prenatal or even preconception injuries sustained by the child. (Preconception injuries might be claimed if, for example, laboratory procedures involving the gametes were thought to have given rise to the damage.) The plaintiff in such a suit would face the difficult task of demonstrating a causal connection between the procedures of in vitro fertilization or embryo transfer and the child's injuries.[38]

Alternatively, a "wrongful life" suit might be brought on behalf of a child born alive but handicapped following in vitro fertilization and embryo transfer. Such a suit would claim that it would be better for a child not to be born at all than to be born in a damaged condition. With one exception,[39] the courts have refused to recognize "wrongful life" as a valid ground for recovery of damages. This refusal appears to stem from a reluctance or inability to assign a monetary value to either impaired existence or nonexistence as a basis for recovery.[40] Even if "wrongful life" were accepted as a valid cause of action in principle, the plaintiff would still face the challenge of showing a causal connection between the procedures employed and the child's injuries.[41]

b. Actions to compensate the parents. Two distinct types of suit might be brought under this general heading. First, it might be claimed that negligently-caused damage to a child conceived by means of in vitro fertilization had caused the parents economic loss and/or emotional distress. Courts have held that the following "wrongful birth" suits stated a valid cause of action:

1. The mother of a severely deformed child brought suit against her physician for his failure to diagnose rubella during pregnancy.[42]

2. Parents brought suit against a physician for failing to diagnose a pregnancy in time to allow the woman to secure an abortion.[43]

3. A pharmacist was sued for mistakenly filling a prescription for the contraceptive Norinyl with a different drug, Nardil, when the woman subsequently became pregnant.[44]

4. A couple brought suit against a physician whose sterilization of the husband failed to prevent the wife's conception of a subsequent child.[45]

If a "wrongful birth" suit were brought because of the birth of a handicapped child following in vitro fertilization, the plaintiff would face the difficulties of demonstrating causation which have been alluded to in the preceding paragraphs.[46]

A second possible cause of action which might be brought by would-be parents on their own behalf is an action for the "wrongful death" of a hoped-for child. All states currently allow actions for wrongful death caused by prenatal injuries if the death occurs following live birth. In addition, many states allow recovery for the prenatal death of a viable fetus.[47] The question raised by in vitro fertilization and embryo transfer is whether the theory of "wrongful death" would be extended by the courts to cover preimplantation human embryos.

Under a somewhat different legal theory -- one which focused on the destruction of the would-be parents' property rather than on the "wrongful death" of an early embryo -- a New York jury recently awarded $50,000 for emotional distress following the intentional destruction of a culture containing gametes from the husband and wife.[48] In the opinion of Flannery and associates, it is unlikely that the courts will ultimately extend the concept of "wrongful death" to include the intentional destruction of a preimplantation embryo.[49] According to Katz, suits charging physician negligence in the unintentional death of an embryo or fetus conceived with the aid of in vitro fertilization are also unlikely to succeed because of the experimental character of the procedure and because of the absence of a clear standard of due care.[50]

3. Compensation for injury. In part because traditional tort concepts seem inapplicable to research involving in vitro fertilization and/or embryo transfer, Katz proposes the establishment of a federal compensation fund to provide monetary redress in the event of injury associated with such research.[51] In her view, the rationale for creation of such a fund is that society has a substantial interest in establishing a program of human in vitro fertilization research and therefore has an obligation to the human subjects who may be injured as a result of their participation in such a program. Any injury which is not clearly unrelated to participation in the in vitro fertilization program would be compensable. The amount of compensation would be determined by calculating the monetary requirements for making the situation of a damaged child or mother equal to that of a normal person, insofar as such calculation is possible. The compensation fund would be financed through premiums paid by researchers or their institutions, by adding a surcharge to hospital bills, or by allocating general revenues to this purpose. The plan would include financial incentives to encourage the exercise of due care by investigators and institutions.

D. Criminal Law

The primary question of criminal law that might arise is whether the act of allowing preimplantation human embryos to die or killing them would constitute the crime of feticide, a species of homicide. After surveying developments in English and American jurisprudence, Katz concludes that the destruction of preimplantation human embryos is not likely to fall within either homicide or feticide statutes.[52]

As noted above, however, state statutes enacted to regulate research involving human fetuses may be broad enough to include research involving preimplantation human embryos. For example, one state statute defines the "human conceptus" as "any human organism, conceived either in the human body or produced in an aritificial environment other than the human body, from fertilization through the first 265 days thereafter."[53] The statute continues:

> Whoever uses or permits the use of a living human conceptus for any type of scientific, laboratory research or other experimentation except to protect the life or health of the conceptus, or except as herein provided, shall be guilty of a gross misde meanor.[54]

In summary, aside from HEW regulations governing research supported by the Department, and a very few broadly written state statutes prohibiting research on the human fetus, no state or federal laws apply to human in vitro fertilization. However, Supreme Court decisions recognizing a fundamental right to privacy in marital relations and reproductive activity suggest that married couples might successfully assert a right of access to in vitro fertilization and embryo transfer as a means of bearing their own children. The government would have to demonstrate a compelling state interest (e.g., protecting the health and safety of mothers and offspring) to justify restricting such access. The government need not, however, provide federal support for such procedures. In the research context, the government may regulate the manner in which research is conducted, especially if the research is supported by funds and it involves human subjects. Questions about legal responsibility for the care of the offspring cannot be answered with clarity. Analogous statutory and case law in the field of artificial insemination suggests that the

law in this area is confused, at best. Similarly, questions about liability and compensation for injuries to the mothers and offspring need to be addressed.

FOOTNOTES

NOTE: The two papers prepared for the Board and cited often throughout are: Dennis M. Flannery, et al., "Legal Issues Concerning In Vitro Fertilization" (hereinafter cited as, Flannery et al.) and Barbara F. Katz, "Legal Implications of In Vitro Fertilization and Its Regulation" (hereinafter cited as Katz).

1. 45 CFR §46.204(d).

2. 39 Federal Register 30650, August 23, 1974.

3. 45 CFR §46.205.

4. 45 CFR §46.202(a)(1).

5. Public Law 93-348, 88 Stat. 348, July 12, 1974.

6. 45 CFR §46.201(b).

7. Katz, pp. 6-10; cf. Flannery et al., pp. 48-49.

8. Katz, pp. 6-10; cf. Flannery et al., pp. 48-49.

9. Flannery et al., pp. 5-6; Katz, pp. 42-44.

10. Flannery et al., p. 35.

11. Maher v. Roe, 432 U.S. 464, 478 (1977).

12. Flannery et al., p. 35.

13. Maher v. Roe, 432 U.S. 464, 474 (1977).

14. Skinner v. Oklahoma, 316 U.S. 535 (1942).

15. Flannery et al., p. 10.

16. Griswold v. Connecticut, 381 U.S. 479 (1965).

17. Eisenstadt v. Baird, 405 U.S. 438, 453 (1972); see also, Carey v. Population Services International 431 U.S. 678 (1977).

18. Flannery et al., pp. 38-40; Katz, p. 49.

19. Flannery et al., p. 40.

20. Id. at 41-42.

21. Id. at 42-44.

22. Id. at 45, n. 68.

23. Id. at 45-46.

24. Id. at 46-47; Katz, p. 49.

25. Flannery et al., pp. 47-54.

26. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Institutional Review Boards: Report and Recommendations, DHEW Publication No. (OS) 78-0008, U.S. Government Printing Office, Washington, D.C., 1978, p. 78. (Discussed in Flannery et al., p. 58 et seq.)

27. Id. at 79.

28. Id.

29. Flannery et al., p. 60; Katz, pp. 45-46.

30. Flannery et al., p. 61.

31. Id., pp. 61-63; Katz, p. 49.

32. Flannery et al., pp. 63-65.

33. 45 CFR §46.203(d).

34. Flannery et al., pp. 70-72.

35. 28 U.S.C. §1346(b); Flannery et al., pp. 73-74.

36. 28 U.S.C. §2680(a).

37. Flannery et al., pp. 76-82.

38. Katz, p. 15; Flannery et al., pp. 85-86.

39. Park v. Chessin, 60 App.Div.2d 80, 400 N.Y.S.2d 110 (1978).

40. Katz, p. 18; Flannery et al., p. 87.

41. Katz, p. 18.

42. Jacobs v. Theimer, 519 S.W.2d 846 (Texas 1975); cited by Katz, pp. 18-19.

43. Ziemoa v. Sternberg, 400 N.Y.2d 110 (1977); cited by Katz, p. 19.

44. Troppi v. Scarf, 187 N.W.2d 511 (Mich. 1971); cited by Katz, p. 19. and Flannery et al., p. 88.

45. Doerr v. Villate, 220 N.E.2d 767 (Ill. 1966); cited by Katz, p. 19.

46. Katz, pp. 19-20; Flannery et al., pp. 88-89.

47. Flannery et al., p. 88; Katz, pp. 29-30.

48. Del Zio v. Presbyterian Hospital, 1974 Civ. 3588 (S.D.N.Y. 1978).

49. Flannery et al., p. 88.

50. Katz, p. 27.

51. Katz, pp. 32-37.

52. Katz, pp. 21-25.

53. Minn. Stat. Ann. §145.521, section 2 (West 1977); cited by Flannery et al., n. 19.

54. Minn. Stat. Ann. §145.522 (West 1977); cited by Flannery et al., n. 19.

CHAPTER V: REVIEW OF PUBLIC ATTITUDES

A. Responses Received by the EAB

Between September 15 and December 15, 1978, the Ethics Advisory Board held eleven public hearings on the question of federal support of research involving human *in vitro* fertilization (IVF) in order to afford an opportunity for members of the public to present their views. In all, several thousand hearing notices were sent to professional organizations, public interest groups, universities, clergy, and individuals. Everyone who requested to appear was heard; 179 individuals presented testimony in hearings in Bethesda (Maryland), Boston, Seattle, San Francisco, Atlanta, Kansas City, Detroit, Philadelphia, Denver, Dallas and New York City. Eighteen people preferred to submit formal written testimony in lieu of oral presentation. In addition, the Board received over 2000 letters and postcards, some of which were forwarded from President Carter and Secretary Califano.

Transcripts of all formal presentations (both oral and written) have been distributed to members of the Board and are available to the general public from the National Technical Information Service (NTIS). All of the correspondence received by the Board has been duplicated and distributed to members; copies are on file at the office of the EAB and are available for public inspection.

In the arguments and presentations made to the Board, it was evident that many people did not distinguish between basic research involving laboratory fertilization of human ova (IVF) on the one hand, and the subsequent transfer of the resulting embryos to establish

a pregnancy, on the other. Thus, some of the arguments both for and against "in vitro fertilization" referred only to one or another of the procedures under consideration by the Board. At the public hearings, it was often possible to elicit clarification by asking whether a person's statement was intended to apply to both the basic research and the clinical application; this was not the case with respect to written communications. Summaries of the arguments are presented below.

1. Arguments in Favor of Federal Funding. Although there were, of course, many variations on the theme, most of the arguments in favor of federal support of IVF focused on either the risks and benefits of IVF or the rights of investigators and infertile couples: (a) the scientific benefits to be gained; (b) the need for federal regulation; (c) the necessity to evaluate and to reduce the risks inherent in the procedure and the reliance of such research on federal support; (d) freedom of inquiry for scientists; (e) freedom of reproductive choice for infertile couples; and (f) the rights of infertile couples to some return on their taxes paid for general health and welfare.

The majority of individuals who favor federal funding for research involving human IVF stressed the benefits it would produce for the general welfare (e.g., understanding and correcting infertility, preventing birth defects, understanding certain hereditary diseases, furthering the search for a cure for cancer, improving our knowledge of early fetal development, and developing better methods of contraception). A number of witnesses stated that there are many scientific

procedures that can be used for either the benefit or the detriment of mankind; but the possibility for abuse does not in and of itself make their development morally wrong. Many responded to the concern regarding "discards" by noting that fertilized eggs are often lost in the natural process of reproduction. Some stated that it is morally irrelevant whether embryo loss occurs naturally or in a laboratory. Other individuals pointed out that zygote wastage may eventually be eliminated. For example, it may be possible to extract only one ovum at a time, as suggested by Dr. Steptoe (on Meet the Press), once the techniques of fertilization and embryo transfer are improved. Moreover, some public witnesses stated that once the technique of freezing the embryos is perfected, fertilized eggs that are not transferred immediately may be preserved for later attempts at implantation.

Numerous witnesses expressed concern about the possible risks of embryo transfer procedures already being performed in the private sector. A few stressed the need to hold investigators accountable for their actions; others urged federal support of the activities in order to apply regulations to assure that they will be conducted in a responsible manner. They thought that if the government were to fund research and adopt regulations governing the experimentation, investigators receiving non-government money would follow the government regulations.

Some stressed the need for government support to assure greater exploration of animal models and to encourage basic research in human IVF so that the safety and efficacy of the procedure can be evaluated before clinical application of embryo transfer is permitted. A related

argument was that if research is permitted, scientists may be expected to improve the technique of *in vitro* fertilization and embryo transfer so that risks to mother and offspring will be substantially reduced.

Several individuals stressed the responsibility of the government to assure freedom of inquiry. Others urged the government to educate the public about the significance of new scientific discoveries to the public. They were concerned that the development of federal policy with such profound implications might be influenced by a public unnecessarily alarmed by inaccuracies and misinterpretations.

The last set of arguments in favor of federal funding related to the rights of infertile couples as taxpayers and the corresponding duties of the government. A number of individuals felt that since childless couples have paid taxes that subsidize the costs of contraception and childbearing, as well as education and welfare, for other people's children, the government has an obligation to assist them by supporting research and services relevant to their reproductive needs. Some argued that it is the government's responsibility to ensure freedom of choice for women by making both alternatives -- raising a family or remaining childless -- available to all couples.

It was stated that at the present time, adoption is not a viable alternative for childless couples. The waiting list for infants is very long and the cost for international adoption is exhorbitant and limited. There was additional testimony, however, that even if adoption procedures could be improved, problems would remain; adoption does not satisfy the very strong desire to bear one's own child. Some even suggested that

the unfulfilled desire to bear children threatens the mental health of women and the stability of marriages. They argued that infertility is a disorder requiring medical intervention, and that the government has a responsibility to make such health care available to all citizens. Since the government funds therapeutic abortions when bearing a child would threaten the life or health of the mother, they noted, the government ought to fund "therapeutic conception" as well. Some elaborated on this argument, stating that government funding is necessary to assure that the option of having a child through in vitro fertilization is available to poor women as well as to those who are able to purchase the option in the private sector.

2. Arguments Opposed to Federal Funding. In general, the arguments against federal support of IVF and embryo transfer stemmed from five major concerns: (a) the moral status of the embryo; (b) questions of safety; (c) funding priorities; (d) decreasing ability to limit more objectionable procedures; and (e) detrimental social and psychological effects on offspring, family and physicians.

The most frequently articulated argument against federal funding of IVF was based on the moral status of the fertilized egg and embryo. Proponents of this argument believed that human life should be respected from the moment of fertilization. They argued that deliberately to create human life merely for experimental purposes with no intent or expectation of sustaining such life is immoral.

Since many fertilized eggs are discarded in the normal process of procreation some proponents of this position said that they might not

oppose *in vitro* fertilization research if a technique could be perfected that would allow the investigators to extract and fertilize only one egg, or freeze for later transfer the embryos which could not be implanted immediately. Others stated that even if such a technique were perfected, it would still be unethical to fund *in vitro* fertilization research because of the immorality of interfering with the natural process of human reproduction.

Many individuals expressed concern about proceeding with embryo transfer in humans without further data concerning its safety. They believed that more should be known about the probability of producing defective embryos. They also thought it important to gain more information concerning level of risk to the women undergoing the procedures. Among opponents of federal funding on the grounds of safety were those who thought that people have a right to take risks by volunteering for research conducted in the private sector, but that it is unethical for the government to approve and support IVF and embryo transfer in humans before the risks and benefits have been more fully evaluated.

A large number of persons opposed government funding of IVF and embryo transfer because they believe it is not an important national priority. Various other needs were suggested as having greater claims upon government funds. A favorite alternative was research to develop methods of preventing and treating disorders (such as pelvic infectious diseases) that result in the tubal occlusion giving rise to demands for IVF. Others indicated that funds would be better spent in improving fertility control and in learning to prevent or treat birth defects

and genetic abnormalities. Still others stressed society's responsibility toward those children already in existence who have been abused or abandoned. Programs encouraging adoption should have higher priority than IVF. There were also those who believed it inappropriate to fund IVF when the majority, they were certain, opposed such research on deeply-felt ethical or religious grounds. The government should not spend public money for experiments so clearly in conflict with the basic commitments of many of the citizens.

Some expressed a fear that approving policies that permit researchers consciously to intend human life to die in vitro could lead to an inability to draw barriers to policies that allowed more obviously objectionable occasions for humans to end the life of other humans. Some proponents of this argument believed that the selective destruction of undesirable fertilized eggs might contribute to the creation of a eugenic program controlled by some officially condoned elite. There was even the fear that barriers would fall to the creation of half-animal, half-human hybrids or chimeras.

A variety of harmful consequences to the psychological and social wellbeing of those involved in IVF were cited as reasons for not funding such research. Fears were expressed that children born through in vitro fertilization would initially be subject to considerable noteriety and be unable to escape a continuing stigma. There was concern that IVF might endanger the family by reducing the human act of reproduction to an artificial or mechanical laboratory procedure. An even greater threat to the family would be the possible use of surrogate mothers

and extra-marital donors of genetic material. This set of reasons for opposing government funding of IVF included the dehumanizing of scientists and doctors involved in the research who must dispose of the human embryos. Another possible consequence cited as a reason for opposing funding was the possible exploitation of uneducated, poor and minority women.

B. Public Opinion Surveys

Since the birth of Louise Brown on July 25, 1979, both the Gallup and Harris survey organizations have conducted polls providing the clearest indication available of United States public opinion concerning IVF. The Gallup survey included reactions of both men and women. The Harris survey, conducted August, 1978 for Parents magazine, polled 1501 representatively selected American women. Both polls revealed that majority opinion favors IVF. However, most women in the Harris survey wanted IVF prohibited until further testing had established its safety, and they opposed federal funding of research on IVF.

Gallup reported that 60% of both men and women "favored" the operation. Of persons who could fully explain the procedure, 75% approved, indicating that more knowledge of IVF led to greater acceptance. Approval was even higher among the women in the Harris poll. Eighty-five percent said that the procedure should be an option for couples otherwise unable to have children.

As to whether Americans would be willing to avail themselves of the operation, the two polls reported that a majority would do so. Gallup found 53% of Americans generally would undergo the procedure. Harris reported that 58% of women of childbearing age would consider using IVF.

More specifically defined groups among childbearing women produced even more favorable attitudes: 61% of younger women, age 18-39, approved of IVF, as did 66% of the women actually planning to have children.

While most women in the Harris survey approved of IVF as a legitimate option, when they were asked if they couldn't have children would they prefer adoption or IVF, more than twice as many chose adoption (57%) as IVF (21%). Furthermore, a healthy majority (63%) wanted IVF to be banned as standard medical practice until further research had determined whether the operation increased the likelihood of birth defects. (Only 24% wanted IVF available immediately.) Interestingly, although most women wanted further testing of IVF, half (50%) opposed federal funding of such research.

PUBLIC WITNESSES

ATLANTA, GEORGIA

Catherine S. Amos, O.D.
Private Citizen
Birmingham, Alabama

Mrs. Barbara Holmes
Adoption Consultant
Department of Human Resources
State of Georgia
College Park, Georgia

Joseph P. Williams, M.D.
Private Citizen
Athens, Georgia

BETHESDA, MARYLAND

Mr. and Mrs. Dennis R. Grills
Private Citizens
Hendersonville, Tennessee

William F. Colliton, Jr., M.D.
National Right to Life
Washington, D.C.

Ted Howard
Co-Director, People's
Business Commission
Washington, D.C.

John Gorby
Right to Life and Right to Die
Committee of the American
Bar Association

BOSTON, MASSACHUSETTS

Tabitha Powledge, M.S.
Hastings Institute of Society,
Ethics, and the Life Sciences
Hastings-on-Hudson, New York

Martha Robb
Science for the People
Cambridge, Massachusetts

Joseph Stanton, M.D.
Associate Clinical Professor
of Medicine
Tufts University School
of Medicine
Boston, Massachusetts

Joyce T. Tuomy
Member, Town Meeting
Framingham, Massachusetts

Rabbi Dr. Samuel J. Fox
President,
Massachusetts Council of Rabbis
Lynn, Massachusetts

Barbara Manning
Private Citizen
Belmont, Massachusetts

Charles Leavitt Sullivan, M.D.
Private Citizen
West Newton, Massachusetts

Reverend Paul J. Murphy, S.J.
Professor of Theology (retired)
Boston College
Newton, Massachusetts

Honorable William X. Wall
Senator
2nd Essex and Middlesex District
Boston, Massachusetts

A. Bruce MacDonald, Ph.D.
Professor and Head,
Department of Microbiology
University of Massachusetts
Amherst, Massachusetts

BOSTON (CONT.)

Joan Ghio
Private Citizen
Burlington, Massachusetts

Tina and Peter Golden
Private Citizens
Roslindale, Massachusetts

Anthony Sbarra, Ph.D.
Director of Clinical Laboratories
and Research
St. Margaret's Hospital for Women
Boston, Massachusetts

Debra and Kevin Canniff
Private Citizens
Belmont, Massachusetts

William A. Lynch, M.D.
Massachusetts Catholic Conference,
National Federation of Catholic
Physicians Guild
Milton, Massachusetts

Jonathan King, Ph.D.
Coalition for Responsible Genetic
Research
Cambridge, Massachusetts

Joseph A. Zdonczyk
Private Citizen
Wolcott, Connecticut

Rosemary and Charles Hersey
Private Citizens
Belmont, Massachusetts

Ruth Hubbard, Ph.D.
Professor of Biology
Harvard University
Cambridge, Massachusetts

Randolph W. Seed, M.D.
Richard G. Seed, Ph.D.
Reproduction and Fertility
Clinic, Inc.
Elgin, Illinois

DALLAS, TEXAS

Frank E. Ladwig
Associate Professor & Director,
Social Work Program
College of Santa Fe
Dallas, Texas

John McDonald
Private Citizen
Houston, Texas

Ms. Ann Ford
Private Citizen
Dallas, Texas

L.C. Powell, M.D.
Professor of Obstetrics &
Gynecology
University of Texas
Medical Branch
Galveston, Texas

Ms. Brenda Marshall
Private Citizen
Dallas, Texas

Ms. Isabel Shavers
Private Citizen
Dallas, Texas

Mrs. Jim Welsh, R.N.
Private Citizen
Dallas, Texas

Mrs. Leon (Ann) Lesniak
Private Citizen
Dallas, Texas

Desiree Inget
Private Citizen
Austin, Texas

Reverend Joseph T. Leonard, S.J.
Catholic Diocese of Dallas
Irving, Texas

DALLAS (CONT.)

Dr. Michael M. Donovan
Chief Surgeon, Shriners Hospital
for Crippled Children and
Clinical Professor at University
of Texas Medical School at Houston
Houston, Texas

Dr. Joseph Graham
Professor of Philosophy
University of St. Thomas
Houston, Texas

John McDonald
Private Citizen
Houston, Texas

Reverend Steve Shiffman
Private Citizen
Atlanta, Georgia

Mrs. Sharon Johns
Private Citizen
Garland, Texas

La Neil Wright
Governor's Commission on the
Status of Women
Dallas, Texas

Roy J. Heyne, Jr., M.D.
Assistant Professor of Pediatrics
University of Texas -- Health Science
Center, Southwestern Medical School
Irving, Texas

Lewis E. Berry, Jr.
Attorney
Houston, Texas

Reverend Ed Robinson
Biology Department
Bishop Lynch High School
Dallas, Texas

T.I. Ballinger, M.D.
Private Citizen
Fort Worth, Texas

John Crosby
Philosophy Department
University of Dallas
Irving, Texas

Josef Seifert, Ph.D.
Associate Professor of Philosophy
and Director of Graduate
Philosophy Program
University of Dallas
Irving, Texas

J. Patrick McCarty, M.D.
University of Texas
Southwestern Medical School
Dallas, Texas

L. Russell Malinak, M.D.
Baylor College of Medicine
Houston, Texas

Mr. Louis A. Shone III
Private Citizen
Dallas, Texas

DENVER, COLORADO

Vicar James Cotter
Bethlehem Lutheran Church
Lakewood, Colorado

Virgil Dechant
Supreme Knight, Knights of
Columbus
Aurora, Colorado
(Testimony presented by William
Small)

Caroline Reutter, M.D.
Women's Medical Association

DENVER (CONT.)

Frank Morriss
Contributing Editor
The Wanderer
St. Paul, Minnesota

Angeline D. Heaton, M.D.
President, American Medical
Women's Association
Colorado Commission on Women
Denver, Colorado

George Betz, M.D.
School of Medicine
Professor of Obstetrics &
Gynecology
Denver, Colorado

Earl F. Dodge
President, Colorado Right to
Life Committee
Denver, Colorado

Father Gerald Sullivan
Catholic Social Services
Casper, Wyoming

Dr. Thomas C. Washburn
University of Colorado Medical
Center
Denver, Colorado

Joseph D. McInerney
Center for Education in Human
and Medical Genetics
Boulder, Colorado

Reverend Alex Lukens, Jr.
Episcopal Priest and Hospital
Chaplain

Rand L. Kannenberg
Private Citizen
Colorado Springs, Colorado

Andrew D. Keller
Private Citizen
Longmont, Colorado

Richard P. Francis, Ph.D.
Professor of Ethics
University of Colorado
Colorado Springs, Colorado

A.D. Lodwick
Private Citizen
Denver, Colorado

Father Nicholas Persech
Dean of Theology School at
St. Thomas Seminary
Denver, Colorado

Ruth Dolan
President, Denver Metro
Chapter of Colorado
Right to Life Committee
Denver, Colorado

Barbara Zibbideo
Private Citizen
Greeley, Colorado

Carol Lees
Private Citizen
Denver, Colorado

Jerry Durnford
Private Citizen
Denver, Colorado

Mary Rita Urbish
Colorado Right to Life
Denver, Colorado

Janet Foster
Private Citizen
Denver, Colorado

DETROIT, MICHIGAN

Diane Fagelman
Private Citizen
Pontiac, Michigan

Father Walter A. Markowicz
Archdiocese of Detroit
Detroit, Michigan

David Favre
Professor of Law
Detroit College of Law
Detroit, Michigan

Sister Betty Gaiss
Office of Health Affairs
Diocese of Lansing
Lansing, Michigan

Dr. Hans A. Schieser
Associate Professor of Education
DePaul University
Chicago, Illinois

David Thompson
Private Citizen
Detroit, Michigan

Judy Jones
Private Citizen
Farmington Hills, Michigan

Frank Teskey
Regional Director
Catholics United for Faith
Royal Oak, Michigan

Patricia Nixon
President, Educational Center
for Life Values
Birmingham, Michigan

Tom Evans, M.D.
Chairman, Department of
Obstetrics and Gynecology
Wayne State University
Detroit, Michigan

KANSAS CITY, Missouri

Helen Froesman
Archdiocese of Kansas City
Kansas City, Kansas

Mrs. Jane Clark
Private Citizen
Overland Park, Kansas

Mr. Kevin Conley
Private Citizen
Kansas City, Kansas

Mrs. Ginger Drybread
Private Citizen
Olathe, Kansas

Right Reverend Jerome Hanus
Abbot, Order of St. Benedict
Conception Abbey
Conception, Missouri

Carolyn Harris
Diocesan Council of Catholic
Women
Kansas City, Missouri

Linda J. Borman
Private Citizen
Council Bluffs, Iowa

Mr. Norman Bettis
PRO-Family Forum
Kansas City, Missouri

Ann O'Donnel, R.N.
Missouri Citizen for Life
St. Louis, Missouri

Reverend Alberts S. Morzczewski,
O.P., Ph.D.
President, Pope John XXIII
Medical-Moral Research and
Education Center
St. Louis, Missouri

Fred Bolton
Pro-Life and Life Advocates
of Wyandotte County
Kansas City, Kansas

Shirley Woods
Saint Peters Pro-Life Group
Kansas City, Kansas

Sister Aerab Pottinger
Embryologist
St. Mary's Hospital
Kansas City, Missouri

Mary Miller
Chairperson, Eastern Kansas
Right to Life

Mr. Terry Richards
Private Citizen
Kansas City, Kansas

PHILADELPHIA, PENNSYLVANIA

Councilman James J. Tayoun
Philadelphia, Pennsylvania

Dr. William Mellman
Professor and Chairman, Department
of Human Genetics
University of Pennsylvania
Philadelphia, Pennsylvania

Edward Wortham, Ph.D.
Assistant Professor of
Biological Sciences
Old Dominion University
Norfolk, Virginia

Brother Patrick Ellis
President
LaSalle College
Philadelphia, Pennsylvania

Edward Stemmler, M.D.
Dean, School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Mrs. Peter Hoffman
Private Citizen
Wallingford, Pennsylvania

Mr. Sam A. Banks
President, Dickinson College
Carlisle, Pennsylvania

Mrs. Patricia Provost
Private Citizen
Bryn Mawr, Pennsylvania

Mrs. Adelaide Bracalenti
Private Citizen
Woodlyn, Pennsylvania

Ms. Donna Draus
Private Citizen
Philadelphia, Pennsylvania

Emanuel Heigelman, D.O.
Private Citizen
Philadelphia, Pennsylvania

Mr. Ronald Zukin
Private Citizen
Westchester, Pennsylvania

Mrs. Ann Schecter
Private Citizen
Bala Cynwyd, Pennsylvania

Joseph Gambescia, M.D.
St. Agnes Hospital
Philadelphia, Pennsylvania

Carl Stark, M.D.
Mayor
Wytheville, Virginia

Mrs. Eileen Meyers
Co-Chairman, Stop ERA in
Pennsylvania
Cornwells Heights, Pennsylvania

Ms. Malana Petite
Women Ad Hoc Health Commission
Philadelphia, Pennsylvania

David E. Price, M.D.
Special Assistant to Provost
and Director of Research
Programs
Johns Hopkins School of Medicine
Baltimore, Maryland

Reverend James J. McCartney
(on behalf of)
Warren T. Reich, Ph.D.
Georgetown University School of
Medicine
Washington, D.C.

Deborah DeBardeleben
President, L.I.F.E. America
Quanyville, Pennsylvania

Mr. J.P. Stanton
Director, Pennsylvania Right to Life
Jenkintown, Pennsylvania

Mr. Harold W. Luebs
Administrator, Children's Hospital
of Pittsburgh
Pittsburgh, Pennsylvania

George Isajiw, M.D.
Private Citizen
Upper Darby, Pennsylvania

Mr. Robert Korsan
Private Citizen
Philadelphia, Pennsylvania

Jay W. MacMoran, M.D.
Chairman, Commission of Medicine,
Religion and Bioethics
Pennsylvania Medical Society
Lemoyne, Pennsylvania

Dr. Donald Self
Bioethicist & Director
of Human Values in Medicine
Eastern Virginia Medical School
Norfolk, Virginia

P. Apostolidis, M.D.
Clinical Associate Professor of
Gynecology at Jefferson Medical
College
Philadelphia, Pennsylvania

John M. Levinson, M.D.
President-Elect of the Delaware
Obstetrical Society
Wilmington, Delaware

Mr. Gizzi
Private Citizen
Mawhaw, New Jersey

Gino Pappola, M.D.
President, International
Federation of Catholic
Medical Associations
Philadelphia, Pennsylvania

Ms. Katherine Gillet
Private Citizen
Philadelphia, Pennsylvania

Reverend Francis Meehan
Archdiocese of Philadelphia
Philadelphia, Pennsylvania

Allen Enders, Ph.D.
Researcher
University of California
Davis, California

Raymond Dennehy, Ph.D.
Department of Philosophy
University of San Francisco
San Francisco, California

Donna Daentl, M.D.
University of California
San Francisco, California

Ann K. Brothers, Ph.D.
Assistant Professor
Department of Zoology
University of California
Berkeley, California

Mary Anne Schwab
Legislative Information
Chairman
National Council of Catholic
Women
San Francisco, California

Diane Coleman
Private Citizen
San Francisco, California

David Schaeffer
Private Citizen
San Francisco, California

Edward E. Wallach, M.D.
Director, Obstetrics and Gynecology
Pennsylvania Hospital & Professor
Obstetrics and Gynecology,
University of Pennsylvania School
of Medicine
Philadelphia, Pennsylvania

Francis Felice
Professor of Biology
University of San Francisco
Deacon, Archdiocese of San Francisco
San Francisco, California

Philip Martin
Private Citizen
San Francisco, California

Deborah Streeter
Private Citizen
Berkeley, California

Mr. Paul Herbert
Private Citizen
San Francisco, California

Judy Johnson
Private Citizen
San Francisco, California

Leonie Watson, M.D.
National Doctors for Life
San Francisco, California

Mitchell S. Golbus, M.D.
University of California
San Francisco, California

Roger A. Pedersen, Ph.D.
Professor of Radiobiology
University of California
Medical Center
San Francisco, California

Robert Glass, Ph.D.
University of California
Berkeley, California

Ms. Nancy Fund
Research Associate, Health Services
Research, Stanford University

Mrs. Norge Humeniuk
Private Citizen
Mills Valley, California

Evelyn Eaton, Ph.D.
Sociology (Free-lance)

Mrs. Arlene Kessler
Private Citizen
Oakland, California

David Galvin
Private Citizen
Oakland, California

Mr. Robert Kessler
Private Citizen
Oakland, California

Ms. Lois Bogarot
Private Citizen
Redwood City, California

Bruce Hilton, Ph.D.
National Center for Bioethics
Berkeley, California

Lynn Szwabinsky
Private Citizen
Concord, California

George Maloff, M.D.
Pro-Life Medical Association
of California
San Francisco, California

SEATTLE, WASHINGTON

Dr. Lawrence Karp
Associate Professor of Obstetrics
and Gynecology
University of Washington
Seattle, Washington

Lois Lundquist
Private Citizen
Issaquah, Washington

Joan Ramos
Private Citizen
Seattle, Washington

Reverend Stanley Stefancic
East Shore Unitarian Church
Bellevue, Washington

Janice Rowe
Private Citizen
Seattle, Washington

Robert E. McIntosh, M.D.
Private Citizen
Seattle, Washington

Margaret K. Ose
Private Citizen
Mercer, Island, Washington

Dale Beasley
Department of Science
St. Philomena School
Des Moines, Washington

Mrs. Cynthia Bortz
Program Assistant
Department of Obstetrics &
Gynecology
University Hospital
Seattle, Washington

Connie Miller
Private Citizen
Seattle, Washington

Lex Mottl, M.D.
Virginia Mason Hospital
Seattle, Washington

Donald E. Moore, M.D.
Assistant Professor and Director
Division of Reproductive Endocrinology
and Infertility
University Hospital
Seattle, Washington

Dr. Richard M. Soderstrom
Past President of the American
Association of Laparoscopy
Seattle, Washington

Rev. Joseph C. Frisch, Ph.D., S.T.D.
Philosophy Department
College of Saint Teresa
Winona, Minnesota

Nancy J. Schmitt
Adoption Research Council
Potomac, Maryland

Michael A. Goheen
Private Citizen
Kalamazoo, Michigan

Perry Stearns, M.D.
Wayne County Department of Health
Eloise, Michigan

Susan L. Heine & John D. Heine
Private Citizens
Annandale, Virginia

Dona B. Morris
Private Citizen
Arlington, Virginia

Rev. Charles McConnell
Salem Bible Fellowship Church
Allentown, Pennsylvania

Connie Brewer
Private Citizen
La Mirada, California

Amitai Etzioni
Director, Center for Policy Research
Professor of Sociology
Columbia University
New York, New York

James H. Sammons, M.D.
Executive Vice-President
American Medical Association
Chicago, Illinois

John Hoaglund
Private Citizen
Newport News, Virginia

Maureen E. Webb
Assistant Professor in Biological Science
Holy Name College
Oakland, California

Walter Funk
Chairman, Department of Health
West Chester State College
West Chester, Pennsylvania

Laurence B. McCullough, Ph.D.
Assistant Professor
College of Medicine
Texas A & M University
College Station, Texas

Dr. William R. Cunnick
President, American Social Health Association
Palo Alto, California

Mary Stirling
Private Citizen
Mountaintop, Pennsylvania

Paul Ramsey
Professor of Religion
Princeton University
Princeton, New Jersey

Dolores R. Lear
Private Citizen
Kansas City, Missouri

CHAPTER VI: SUMMARY AND CONCLUSIONS

It is now technically possible to fertilize a human egg outside the body of a woman and then transfer the fertilized egg (sometimes called a blastocyst or preimplantation embryo) back into the woman to establish a pregnancy. For some women, in vitro fertilization may be the only way to bear children of their own. It does not appear, however, that the procedure for achieving pregnancy by this means is yet very effective; the best available data indicate that a number of attempts have been necessary before a pregnancy in a particular woman can be established, if at all. In addition, many questions remain as to the safety of the procedure for the offspring. Nevertheless, there is reason to believe that clinics may soon be established, both in this country and abroad, where in vitro fertilization and embryo transfer will be offered as "therapy" for infertile couples.

The Board is required by HEW regulations to review research proposals involving human in vitro fertilization and advise the Secretary as to their "acceptability from an ethical standpoint."* This phrase is broad enough to include at least two interpretations: (1) "clearly ethically right" or (2) "ethically defensible but still legitimately controverted." In finding that research involving human in vitro fertilization is "acceptable from an ethical standpoint" the Board is using the phrase in the second sense; the Board wishes to emphasize that it is not finding that the ethical considerations against such research are insubstantial. Indeed, concerns regarding the moral status of the embryo and the potential long-range consequences of this research were among the most difficult that confronted the Board.

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*45 CFR 46.204(d)

In its deliberations on human in vitro fertilization, the Board confronted many ethical, scientific and legal issues. Among the more difficult were the following: (A) the moral status of the embryo; (B) the safety and efficacy* of the procedure; (C) the potential long-range adverse effects of such research; and (D) the appropriateness of Departmental support.

A. After much analysis and discussion regarding both scientific data and the moral status of the embryo, the Board is in agreement that the human embryo is entitled to profound respect; but this respect does not necessarily encompass the full legal and moral rights attributed to persons. In addition, the Board noted the high rate of embryo loss that occurs in the natural process of reproduction. It concluded that some embryo loss associated with attempts to assist otherwise infertile couples to bear children of their own through in vitro fertilization may be regarded as acceptable from an ethical standpoint, under certain conditions, as more fully described below.

B. The Board is concerned about still unanswered questions of safety for both mother and offspring of in vitro fertilization and embryo transfer; it is concerned, as well, about the physical and mental health of the children born following such a procedure and about their legal status. Many women have told the Board that in order to bear a child of their own they will submit to whatever risks are involved. The Board believes that while the Department should not interfere with such

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*By "efficacy" the Board means not only whether the procedure can be done but also how efficient it is, e.g., the number of procedures required to achieve the desire result.

reproductive decisions, it has a legitimate interest in developing and disseminating information regarding safety and health so that fully informed choices about reproduction can be made.

C. A number of fears have been expressed with regard to adverse effects of technological intervention in the reproductive process: fears that such intervention might lead to genetic manipulation or encourage casual experimentation with human embryos, or bring with it the use of surrogate mothers, cloning, or the creation of genetic hybrids. Some have suggested that such research might also have a dehumanizing effect on investigators, the families involved, and society generally. (See Chapter III of this report.)

Although the Board recognizes that there is an opportunity for abuse in the application of this technology as other technologies, it concluded that a broad prohibition of research involving human in vitro fertilization is neither justified nor wise. Among the developments warned against by some who testified before the Board, a few (e.g., the cloning of human beings and the creation of animal/human hybrids) are of uncertain or remote risk. Other possible developments, such as the use of surrogate mothers, may be contained by regulation or legislation. Other abuses may be avoided by the use of good judgment based upon accurate information of the type collected by the Board and now being disseminated in this report. Finally, where reproductive decisions are concerned, it is important to guard against unwarranted governmental intrusion into personal and marital privacy.

D. The question of Federal support of research involving human in vitro fertilization and embryo transfer was troublesome for the Board in

view of the uncertain risks, the dangers of abuse and because funding the procedure is morally objectionable to many. In weighing these considerations, the Board noted that the procedures may soon be in use in the private sector and that Departmental involvement might help to resolve questions of risk and avoid abuse by encouraging well-designed research by qualified scientists. Such involvement might also help to shape the use of the procedures through regulation and by example. The Board concluded that it should not advise the Department on the level of Federal support, if any, of such research; but it concluded that Federal support, if decided upon after due consideration of all that is at issue, would be acceptable from an ethical standpoint.

Evidence presented to the Board indicates that human in vitro fertilization and embryo transfer techniques may, in the near future, be employed throughout the world in both research and clinical practice settings. The Board believes that data from these activities as well as related types of animal research should be collected, analyzed and, when appropriate, given wide public dissemination. Accordingly, the Board recommends in conclusion #4 below, that the Department take the primary initiative in carrying out these functions.

Having carefully weighed diverse ethical points of view and a broad base of scientific considerations regarding human in vitro fertilization and embryo transfer, the Board has concluded that: (1) the Department should consider support of more animal research in order to assess the risks to both mother and offspring associated with the procedures; (2) the conduct of research involving human in vitro fertilization designed to establish the safety and effectiveness of the procedures is ethically acceptable under certain conditions; (3) Departmental support of such

research would be acceptable from an ethical standpoint, although the Board did not address the question of the level of funding, if any, which such research might be given; (4) the Department should take the initiative in collecting, analyzing and disseminating data from both research and clinical practice involving in vitro fertilization throughout the world; and (5) model or uniform laws should be developed to define the rights and responsibilities of all parties involved in such activities.

Finally, the Board is aware of the possibility of research that involves the collection and culture of early human embryos in the laboratory which have been fertilized naturally rather than in vitro. The ethical aspects of such research, which appears to bear a close resemblance to research involving in vitro fertilization, have not been examined by the Board. Therefore it has not reached a conclusion concerning the ethical acceptability of these procedures. However, the Board intends to consider in the near future the need for setting standards for such research.

CONCLUSION (1) THE DEPARTMENT SHOULD CONSIDER SUPPORT OF CAREFULLY DESIGNED RESEARCH INVOLVING IN VITRO FERTILIZATION AND EMBRYO TRANSFER IN ANIMALS, INCLUDING NONHUMAN PRIMATES, IN ORDER TO OBTAIN A BETTER UNDERSTANDING OF THE PROCESS OF FERTILIZATION, IMPLANTATION AND EMBRYO DEVELOPMENT, TO ASSESS THE RISKS TO BOTH MOTHER AND OFFSPRING ASSOCIATED WITH SUCH PROCEDURES, AND TO IMPROVE THE EFFICACY OF THE PROCEDURE.

Discussion: As indicated in Chapter III of the Board's report, available scientific data do not indicate clearly either the relative safety or the efficacy of procedures of in vitro fertilization and

embryo transfer. Some scientists have suggested that in vitro fertilization may result in a higher incidence of abnormal embryos than is associated with the normal reproductive process, although there are no animal data that clearly demonstrate such an effect. Neither are there data that demonstrate an absence of increased abnormality in embryos following in vitro fertilization. The Board feels that additional data should be gathered that might indicate whether abnormal embryos are more likely to result and, if so, whether there is a significant increase in the risk of abnormal offspring actually being born following such procedures.

Experts appearing before the Board agreed that there has been insufficient controlled animal research designed to determine the long-range effects of in vitro fertilization and embryo transfer. The lack of primate work is particularly noteworthy in view of the opportunity provided by primate models for assessing subtle neurological, cognitive and developmental effects of such procedures. The Board has been advised that controlled studies of embryo transfer following in vitro fertilization in animals, designed to include developmental assessments, may be feasible and may permit more confident estimates of the risk to human offspring associated with such procedures.

Information regarding the effectiveness of the procedures for in vitro fertilization and embryo transfer is also lacking. It does not appear possible to predict with reliability the number of laparoscopies and embryo transfers that might be required, or the likelihood of success of the procedure for any couple, given the fact that, to date, only three successes have been reported in humans, and that very limited information is available concerning this work. Such data as are available

suggest that any woman hoping to bear a child through in vitro fertilization is likely to face numerous unsuccessful procedures and delays with no assurance of achieving her goal.

Careful research with animal models might provide a more accurate estimate of the chances of achieving a successful pregnancy. It might also reduce the inconvenience and risk to women of undergoing multiple procedures to establish a pregnancy by improving techniques for recovering ova, identifying embryonic abnormalities and achieving implantation. It is often the case in medicine that, even after therapies are already being applied to humans, investigations continue in animals in order to test further or to improve their safety and effectiveness. The Board believes that the Department should consider support of well-designed animal studies whether or not human research or clinical trials are also in progress.

CONCLUSION (2) THE ETHICS ADVISORY BOARD FINDS THAT IT IS ACCEPTABLE FROM AN ETHICAL STANDPOINT TO UNDERTAKE RESEARCH INVOLVING HUMAN IN VITRO FERTILIZATION AND EMBRYO TRANSFER PROVIDED THAT:

A. IF THE RESEARCH INVOLVES HUMAN IN VITRO FERTILIZATION WITHOUT EMBRYO TRANSFER, THE FOLLOWING CONDITIONS ARE SATISFIED:

   1. THE RESEARCH COMPLIES WITH ALL APPROPRIATE PROVISIONS OF THE REGULATIONS GOVERNING RESEARCH WITH HUMAN SUBJECTS (45 CFR 46);

   2. THE RESEARCH IS DESIGNED PRIMARILY: (A) TO ESTABLISH THE SAFETY AND EFFICACY OF EMBRYO TRANSFER AND (B) TO OBTAIN IMPORTANT SCIENTIFIC INFORMATION TOWARD THAT END NOT REASONABLY ATTAINABLE BY OTHER MEANS;

3. HUMAN GAMETES USED IN SUCH RESEARCH WILL BE OBTAINED EXCLUSIVELY FROM PERSONS WHO HAVE BEEN INFORMED OF THE NATURE AND PURPOSE OF THE RESEARCH IN WHICH SUCH MATERIALS WILL BE USED AND HAVE SPECIFICALLY CONSENTED TO SUCH USE;

4. NO EMBRYOS WILL BE SUSTAINED IN VITRO BEYOND THE STAGE NORMALLY ASSOCIATED WITH THE COMPLETION OF IMPLANTATION (14 DAYS AFTER FERTILIZATION); AND

5. ALL INTERESTED PARTIES AND THE GENERAL PUBLIC WILL BE ADVISED IF EVIDENCE BEGINS TO SHOW THAT THE PROCEDURE ENTAILS RISKS OF ABNORMAL OFFSPRING HIGHER THAN THOSE ASSOCIATED WITH NATURAL HUMAN REPRODUCTION.

B. IN ADDITION, IF THE RESEARCH INVOLVES EMBRYO TRANSFER FOLLOWING HUMAN IN VITRO FERTILIZATION, EMBRYO TRANSFER WILL BE ATTEMPTED ONLY WITH GAMETES OBTAINED FROM LAWFULLY MARRIED COUPLES.

Discussion: This conclusion relates to the ethics of conducting research involving in vitro fertilization in general; it does not address the question of Departmental support of such research. The purpose of this more general conclusion is to provide guidance to Institutional Review Boards and other groups who are asked to review research that will not be supported by HEW.* Whether or not the Department decides

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* Federal law requires all institutions receiving research funds from HEW to establish an Institutional Review Board (IRB) to review biomedical and behavioral research involving human subjects. (Public Law 93-348). The Department, in implementing that law, requires all such research conducted at an institution to be reviewed by the IRB, whether or not the research is supported by HEW.

to provide funds for such research, the Board wishes to express its views regarding the conduct of human in vitro fertilization and embryo transfer, so that review groups may benefit from the deliberations of the Board as they conduct their own review of specific research proposals.

As emphasized above, the Board believes that much remains to be learned about the safety and effectiveness of these procedures before they can be considered standard, accepted medical practice. Research designed to provide reliable data regarding safety and efficacy is acceptable from an ethical standpoint if conducted within the constraints indicated above. In the case of research involving embryo transfer, the Board intends not only that the gametes be obtained from lawfully married couples but also that the embryo be transferred back to the wife whose ova were used for fertilization.

The Board also discussed research designed primarily to establish safety and efficacy but which may, in addition, obtain information of scientific importance unrelated to in vitro fertilization and embryo transfer. The Board believes that such research, if performed as a corollary to research designed primarily to establish safety and efficacy of in vitro fertilization and embryo transfer, would also be acceptable from an ethical standpoint.

CONCLUSION (3) THE BOARD FINDS IT ACCEPTABLE FROM AN ETHICAL STANDPOINT FOR THE DEPARTMENT TO SUPPORT OR CONDUCT RESEARCH INVOLVING HUMAN IN VITRO FERTILIZATION AND EMBRYO TRANSFER, PROVIDED THAT THE APPLICABLE CONDITIONS SET FORTH IN CONCLUSION (2) ARE MET. HOWEVER, THE BOARD HAS DECIDED NOT TO ADDRESS THE QUESTION OF THE LEVEL OF FUNDING, IF ANY, WHICH SUCH RESEARCH MIGHT BE GIVEN.

Discussion:

1. Departmental support. The Board consciously adopted the language "acceptable from an ethical standpoint" to indicate the limits of its inquiry. Even though the members are aware that ethical considerations pervade decisions regarding the level, if any, of Departmental support of human in vitro fertilization, the Board has concluded that it lacks the resources needed to render meaningful advice with respect to such decisions. The Board, therefore, defers to established political, scientific and administrative procedures for allocating public research funds.

   The Board wishes to note that such decisions have significant ethical dimensions. For example, some believe that research involving human in vitro fertilization should have a relatively low priority at a time when other health needs, arguably more basic in character and long-term in nature, are unmet. Others find such research objectionable either on grounds related to the moral status of the embryo or because it may lead to undesirable genetic interventions or have a long-range adverse effect. (See Chapter III of this report.) Still others believe that research on human in vitro fertilization and embryo transfer should have a high priority because it might help parents overcome physical obstacles to having their own children and ensure the mothers' safety and the normality of offspring.

The Board has found that these and other ethical arguments for and against public funding of research involving human in vitro fertilization, by themselves, are not conclusive. Instead, the Board believes that the questions of whether to fund and at what level should be made in the larger context where all relevant data and arguments -- scientific, political, economic, legal and ethical -- can be considered. In that context questions such as health and safety, availability of funds, and alternative research proposals, must be considered along with the very difficult type of ethical isssues described above which arise in allocation of resources.

2. Research without embryo transfer. As previously noted the risks of producing abnormal offspring are still undetermined; therefore, an important goal would be to gain as much information as possible from well-designed research on in vitro fertilization not involving embryo transfer in humans. The Department should conduct a careful scientific evaluation of the possibility, supported by some expert testimony before the Board, that animal research and studies involving human in vitro fertilization without embryo transfer, over a relatively short period, might substantially increase our knowledge concerning the possible risk of abnormal offspring as well as lead to the development of safe and more effective techniques.

3. Research involving embryo transfer. While initial research efforts designed to gain as much information as possible from animal studies and human research not involving embryo transfer may be desirable, the Board does not wish to discourage planning and preparation that may lead to clinical trials or other forms of research involving embryo transfer. The Department's participation in, or support of, clinical trials is often an effective method to evaluate the safety and efficacy of innovative medical procedures, particularly as the use of the procedures increases.

4. Research for other purposes. Potentially valuable information about reproductive biology, the etiology of birth defects, and other subjects may be revealed through research involving human in vitro fertilization, without embryo transfer, and unrelated to the safety and efficacy of procedures for overcoming infertility. The Board makes no judgment at this time regarding the ethical acceptability of such research nor does it speculate about what research might be sufficiently compelling to justify the use of human embryos. Instead, it notes that applications for support of such research should be submitted to the Board for ethical review in accordance with 45 CFR 46.204(d).

5. Pending Research Application. Given the criteria specified in Conclusion (2) and incorporated in Conclusion (3) for evaluating research involving human in vitro fertilization, and the Board's views about Departmental support of such research, the Board recommends that the Secretary refer the pending application of Vanderbilt University back to the National Institutes of Health for a determination as to whether the proposal meets those criteria and for further review in light of the considerations set forth in this report.

CONCLUSION (4) THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD) AND OTHER APPROPRIATE AGENCIES SHOULD WORK WITH PROFESSIONAL SOCIETIES, FOREIGN GOVERNMENTS AND INTERNATIONAL ORGANIZATIONS TO COLLECT, ANALYZE AND DISSEMINATE INFORMATION DERIVED FROM RESEARCH (IN BOTH ANIMALS AND HUMANS) AND CLINICAL EXPERIENCE THROUGHOUT THE WORLD INVOLVING IN VITRO FERTILIZATION AND EMBRYO TRANSFER.

Discussion: The Board is aware that the most valuable information regarding in vitro fertilization and embryo transfer is likely to come from well-controlled clinical trials. But it is expected that in vitro fertilization and embryo transfer will soon be performed in clinics throughout the world, sometimes without benefit of research design or experimental controls. It would be unfortunate not to have access to the information that might be gained from such clinical experience, notwithstanding the fact that well-designed investigations would be preferable. With that in mind, the Board recommends that every effort

be made to collect whatever information may be elicited from practitioners in this country and abroad. NICHD should also consider suggesting to practitioners a basic protocol for collecting vital information, to which each would be encouraged to add their own observations.

The data from such clinical experience and from research conducted throughout the world should be analyzed along with that derived from animal studies so that individuals contemplating in vitro fertilization and embryo transfer will have access to the best information available regarding risks to both mother and offspring. Timely dissemination of the information would increase the opportunity for investigators, clinicians and propsective patients to be fully informed.

CONCLUSION (5) THE SECRETARY SHOULD ENCOURAGE THE DEVELOPMENT OF A UNIFORM OR MODEL LAW TO CLARIFY THE LEGAL STATUS OF CHILDREN BORN AS A RESULT OF IN VITRO FERTILIZATION AND EMBRYO TRANSFER. TO THE EXTENT THAT FUNDS MAY BE NECESSARY TO DEVELOP SUCH LEGISLATION, THE DEPARTMENT SHOULD CONSIDER PROVIDING APPROPRIATE SUPPORT.

Discussion: The Board is concerned about the ambiguity regarding the legal status of children born following artificial insemination and a similar ambiguity that may surround the legal status of children born following in vitro fertilization and embryo transfer. The Board is also concerned about lack of clarity regarding the legal responsibilities of those who utilize, support, or permit use of such procedures. Because of the complexity of the legal problems involved in new techniques for human reproduction, the Board recommends that a model or uniform law be

drafted that would establish with clarity the rights and responsibilities of donor and recipient "parents", of offspring, and of those who participate in the process of reproduction through new technologies.

The Board urges that such a uniform or model law be drafted by the National Conference of Commissioners on Uniform State Laws, the American Law Institute, or some other qualified body. Because of the complex nature of the subject matter, however, the Board is aware that the task may be a major undertaking and suggests that the Department consider providing funds for drafting the legislation. Since the purpose is to safeguard the health and welfare of children and their families, it appears to be an appropriate project for Departmental support.

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